DEVELOPMENT OF THE MEDICATION NON-ADHERENCE SCALE (MNAS) AND THE MEDICATION NON-PERSISTENCE SCALE (MNPS)

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ABSTRACT

Medication non-adherence and non-persistence are pressing issues in healthcare today. Their resultant health and economic ill-effects are well studied in numerous diseases. To help improve medication adherence and persistence, their effective and efficient measurement is essential. Thus, the purpose of this dissertation was to develop the Medication Non-Adherence Scale (MNAS) and the Medication Non-Persistence Scale (MNPS).

The scales were administered to patrons of three independent community pharmacies in the Southeastern United States. Their responses were anonymously linked to prescription fill data. The MNAS was validated against the past 6 months of prescription fill data, while the MNPS against the past 12 months. The MNAS was also tested against 3 months of prospective data to study its ability to predict future non-adherence.

Confirmatory factor analyses offered evidence for internal consistency reliability, and convergent and discriminant validity. The results indicated a 5 factor solution for the MNAS – worries about side-effects, worries about addiction, worries about cost, lack of perceived need, and unintentional non-adherence – and a single factor solution for the MNPS. Linear regression analyses concluded that the scales demonstrated concurrent validity (MNAS: unstandardized regression coefficient=-0.50 (p<0.001); MNPS: unstandardized regression coefficient=-3.97 (p=0.03)). Another linear regression analysis also offered evidence for the MNAS having predictive validity (unstandardized regression coefficient=-0.62 (p<0.001)). ROC curve analysis

suggested that a score of greater than 16 on the MNAS indicated non-adherence in the past 6 months, and a score of greater than 20 indicated non-adherence in the next 3 months. A score of 1 or higher on the MNPS indicated non-persistence in the past 12 months.

The MNAS was seen to perform better than the Medication Adherence Reasons Scale (MAR-Scale: R^2=0.016, standardized regression coefficient=-0.125; MNAS: R^2=0.043, standardized regression coefficient=-0.208) and the 1986 Morisky scale (R^2=0.018, standardized regression coefficient=-0.134) in estimating concurrent PDC, and better than the Adherence Estimator (AE: R^2=0.010, standardized regression coefficient=-0.099; MNAS: R^2=0.083, standardized regression coefficient=-0.288) in estimating future PDC. These estimates were also statistically significantly different from each other.

Thus, the MNAS and MNPS help fill vital gaps in adherence and persistence measurement, and may be used by healthcare practitioners and researchers to improve patient health.

DEDICATION

This dissertation is dedicated to the people of Mississippi who took the time to respond to my survey. You are awesome.

LIST OF ABBREVIATIONS AND SYMBOLS

Abbreviation	**Description**
A14	Adherence 14
ACE	Angiotensin-converting enzyme
AE	Adherence Estimator®
ARB	Angiotensin-receptor blocker
ASK-20	Adherence Starts and Knowledge-20
AVE	Average variance extracted
BARS	Brief Adherence Rating Scale
BB	Beta-blockers
BBQ	Beliefs and Behaviour Questionnaire
BMQ	Brief Medication Questionnaire
CCB	Calcium channel blocker
CFA	Confirmatory factor analysis
CMS	Centers for Medicare & Medicaid Services
CR	Composite reliability
DUA	Data Use Agreement
DV	Dependent variable
GLM	General Linear Model
HIPAA	Health Insurance Portability and Accountability Act
IV	Independent variable
LM	Lagrange Multiplier
MAM	Medical Adherence Measure
MARS	Medication Adherence Rating Scale
MAR-Scale	Medication Adherence Reasons Scale
MEMS	Medication Event Monitoring System

MID	Unique mailing identifier
MMAS	Morisky Medication Adherence Scale
MNAS	Medication Non-Adherence Scale
MNAS-I-Addiction	Intentional non-adherence due to worries about addiction to the medication
MNAS-I-Cost	Intentional non-adherence due to worries about cost of the medication
MNAS-I-Perceived need	Intentional non-adherence due to lack of perceived need of the medication
MNAS-I-Side-effects	Intentional non-adherence due to worries about side-effects
MNAS-U	Unintentional non-adherence
MNPS	Medication Non-Persistence Scale
MPR	Medication possession ratio
MUAH	Maastricht Utrecht Adherence in Hypertension
NCQA	National Committee for Quality Assurance
NICE	National Institute of Health and Clinical Excellence
PDC	Proportion of days covered
PQA	Pharmacy Quality Alliance
PTID	Unique patient identifier
RAM	Reported Adherence to Medications
ROC	Receiver-operating characteristic
WLSMV	Weighted least squares with mean and variance adjustment

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CHAPTER I:
INTRODUCTION

BACKGROUND

Importance of Studying Medication Adherence and Medication Persistence

It has been estimated that 30-60% of prescribed medicines are not taken as directed.[1,2] Such behaviors usually involve medication non-adherence or medication non-persistence.[2,3,*] Numerous studies have demonstrated the resultant ill-effects of these behaviors. For example, Ho and colleagues identified the adverse effects of non-adherence to medications used to treat diabetes mellitus on all-cause hospitalizations and all-cause mortality.[4] Studies have also shown that discontinuation of relevant medication therapy post myocardial infarction (i.e. aspirin, β-blockers, and statins) can lead to a statistically significant increase in mortality.[5] Sokol et al. concluded that patients with diabetes mellitus, hypertension, hypercholesterolemia, or congestive heart failure who were non-adherent to their medications had statistically significantly greater hospitalizations. Such behavior was also observed to lead to higher overall health care costs.[6] According to the 2011 Express Scripts Drug Trend Report, an excess of $317.4 billion may have been spent due to medication non-adherence in that year.[7] Due to these reasons, such behaviors have been referred to as "the 'other' drug problem".[8] In order to counter this issue, effective and efficient measurement of medication adherence and persistence is necessary.

Measurement of Medication Adherence

Medication adherence has been operationalized in multiple ways. Some of the often used methods are described below.

Direct patient observation. In this method, as the title suggests, patients are directly observed while taking their medications. Such a technique is direct and objective.[9,10,†] This is often considered the ideal method to measure medication adherence, but when used in the outpatient setting or in large studies, its practicality has been questioned.[9,11] Also, as pointed out by Garfield et al.[12], and Osterberg and Blaschke[9], intentionally non-adherent patients may "hide pills in the mouth and then discard them." This may lead to a bias in classification of individuals as adherent or non-adherent.

Drug level in biological fluids / biological assays and biomarkers. These methods detect the presence of the drug, an associated metabolite, or the biomarker in a biological fluid. In the case of biomarkers, markers are added to the biological fluids in order to detect the presence of the drug or associated metabolites.[11] The advantage of these methods is that they are direct and objective techniques of estimating medication adherence[9,10] But using these methods on a routine basis is difficult. Also, as mentioned by Farmer[11], these method do not measure patients' actual medication-*taking* behavior; despite having the required level of the drug or associated metabolite in the biological fluids, the patient may not have consumed the medication as directed. Thus, there is little evidence to suggest that the patient will follow medication-taking directions in the future.[11]

Pill counts. This is one of the most commonly used methods to measure medication adherence in clinical trials.[13] It is also used in clinical practice.[11] Pill counts are considered to be objective and

indirect measures of medication adherence[9,10] This method involves counting the number of dosage units (tablets, capsules, etc.) that are not consumed by a patient at the time of the scheduled check. The percentage of compliance is then calculated by dividing the number of dosage units consumed by the expected number of dosage units that should have been consumed (taking the number of units prescribed and the days' supply into consideration), and multiplied by 100. Despite its relative simplicity, it has a severe disadvantage – patients may discard their dosage units prior to the scheduled check to appear more adherent (e.g. pill dumping). Thus, pill counts often overestimate adherence behavior.[14–17]

Prescription refill records and administrative claims data. The use of these data sources in the measurement of medication adherence has increased drastically with the availability of drug insurance claims data.[11,18–22] Proportion of days covered (PDC) and medication possession ratio (MPR) have been identified as the most appropriate measures of medication adherence using administrative claims data.[23–26] These methods are considered objective but indirect.[9,10] The formulae for measuring PDC and MPR have been given below.[26–29]

$$\text{MPR} = \frac{\text{Sum of the days supply for all fills of the drug in the study period}}{\text{Number of days in the study period}}$$

$$\text{PDC} = \frac{\text{Number of days the patient is covered by the drug in the study period}}{\text{Number of days in the study period}}$$

PDC offers a more conservative estimate.[29] The calculation of PDC takes potential overlaps and gaps in therapy into consideration. Although either of these methods is accepted in pharmacoepidemiology, pharmacoeconomics, and health outcomes research, some limitations exist. While using prescription records as a surrogate of medication-taking behavior, the researcher must make a few assumptions – the data are complete, i.e. all the necessary variables and records are present[11], and a prescription fill indicates that the medication was consumed.[9]

But in reality, unless the data were obtained from a closed system (e.g., a nationalized health care system) there may be individuals who have obtained a prescription fill from a source other than the one available to the researcher (other pharmacy, other health care insurer, etc.), and a prescription fill may not indicate that the medication was consumed.[9] Being cognizant of these assumptions and taking possible steps to prevent invalidation of obtained values is essential.

Electronic monitoring. Electronic monitoring of medication adherence is done by implementing devices that have a microchip built into them. These are classified as objective, but indirect methods.[9,10] An example of such devices is the Medication Events Monitoring System (MEMS) cap.[14] This is a special prescription bottle cap that collects data every time it is opened. The numbers reported by the MEMS cap can be accurate down to the second at which the cap was opened. This device can help collect continuous, and relatively reliable data.[11,14,30] The MEMS caps have been used to measure medication adherence in numerous studies.[14,31–36] Their successful empirical performance has often resulted in them to being called the "gold standard" measure of medication adherence.[14,30,37] They, however, have some drawbacks. Firstly, they are expensive and cumbersome; they require a visit to the location where the data are being collected for downloading information. Secondly, and perhaps more importantly, they measure the times when the bottles were opened and not when the medication was consumed. If a patient simply opens and shuts the cap (unintentionally, or otherwise), a datum is recorded. This could adversely affect medication adherence measurement.[11,12,38]

Self-reporting. Broadly, there are three types of patient self-reporting methods – patient diaries, patient interviews, and questionnaires.[11] In the case of patient diaries, patients are asked to maintain a diary to record their daily medication-taking behavior. Patient interviews are unstructured, potentially unstandardized and non-validated interviews conducted to obtain

medication adherence-related information from patients. On the other hand, questionnaires are structured, standardized, and often formally tested for their psychometric properties. They are used to obtain empirical data about medication adherence from patients.[11] Self-reporting has often been criticized for offering less reliable and valid estimates of medication adherence.[15,19,39–41] These methods cannot be classified as objective or direct.[9,10] Despite this, the National Collaborating Centre for Primary Care and the Royal College of General Practitioners (London, UK), along with National Institute of Health and Clinical Excellence (NICE) commended these measures as being the most appropriate for monitoring medication adherence in clinical practice.[12,42] The primary reason for this is their feasibility, practicality, and simplicity.[9,11,43] In a clinical setting, other, potentially more valid, reliable, and objective measures such as MEMS, bioassays, biomarkers, prescription refill records, pill counts, etc. are often considered impractical and expensive.[12] Such a setting requires an instrument that is quick and easy to administer, and gives immediate results. Only a self-reported questionnaire is capable of such a task.[12] Moreover, a recent review by Shi and colleagues concluded that self-reported measures demonstrate moderate to high correlation with electronically monitored measures of medication adherence, further strengthening the evidence of the capability for these measures.[44] Thus, a self-reported scale is the preferred choice for a health care practice setting administrable measure of medication non-adherence.

Need for a Better Medication Adherence Scale

Disease non-specificity. Currently, the 1986 Morisky scale is the most widely used self-reported measure of medication adherence in the clinical setting.[45] Although commonly used, data supporting its use offer mixed results. Some studies have reported low internal consistency

reliability, while others report acceptable levels.[33,45–49] The primary reason for its popularity is its ability to be used as a disease non-specific instrument.[33,46,48–50] Although the scale was developed in hypertensive patients, it has yielded similar results in other disease conditions.[33,46,48,49] The Morisky scale was updated in 2009 to improve upon its internal consistency.[51] The Morisky Medication Adherence Scale (MMAS) has twice the number of items (as compared to the 1986 version)[‡], and to the best of our knowledge, has only been tested among hypertensive and diabetic patients.[51–55] In 1999, Horne et al. published the Reported Adherence to Medication (RAM) scale.[56] Although this scale too has been used in multiple disease conditions, it has not been found to report beyond moderate psychometric properties.[49,56,57] Another drawback of this scale is that it uses different units of measurement for half of its items.[56] This may lead to difficulties in its interpretation; an important property in a practice setting.

Distinguishing between different reasons for medication non-adherence. In their recent systematic review, Garfield et al. stated the need for a better disease non-specific measure of medication adherence.[12] In doing so, they outlined three desirable characteristics of such a scale – pragmatic (inexpensive, short, non-intrusive, and flexible to the mode of administration), having good psychometric properties (reliable, valid, sensitive, and specific), and having a sound theoretical foundation (use of an appropriate theory).[12] A theoretical foundation is essential. But using an *appropriate* theory is even more important. Virtually every health behavior theory has been tested in the context of medication adherence – social learning theory/social cognitive theory, theory of reasoned action/theory of planned behavior, health belief model, transtheoretical model, etc. – albeit offering inconsistent results.[58–62] Garfield and colleagues argue that the reason for such results is that these theories assume that the medication non-adherence behavior was intentional.[12] They, along with many others in recent years, suggest that

it is important to distinguish between intentional and unintentional non-adherence.[43,50,57,63–69,§] Such a classification can help in distinguishing between the reasons for non-adherence.

Usually, the purpose of measuring medication adherence in a clinical setting is to intervene and improve it. The underlying rationale for non-adherence is very different in the case of intentional and unintentional non-adherers. Thus the intervention techniques needed to improve medication adherence are different as well.[12] In the case of intentional non-adherence, intervention strategies may focus on the physician-patient relationship, implementation of behavioral strategies (using e.g. health behavior models), etc.[43,58,67,70] While in the case of unintentional non-adherence, strategies such as pill-boxes, reminder phone calls, text messages, emails, etc. would be more beneficial.[12,68,**] Studies have used existing scales to distinguish between these two forms of non-adherence. Some studies have used the 1986 Morisky scale, while others have used the RAM scale.[45,50,56,69,††,‡‡] A recent study by Krousel-Wood and colleagues recommends the used of the Morisky Medication Adherence Scale (MMAS) for this purpose.[55] However, as mentioned earlier, this scale has not been tested outside hypertensive and diabetic patients.[51–55] Thus, its applicability is limited.

Garfield et al. recommended the use of the model of accident causation proposed by Reason[§§] to help distinguish between intentional and unintentional medication non-adherence.[12,63,64,71,72] Barber adapted Reason's framework to the context of medication non-adherence.[63,***,†††] According to this model, unintentional non-adherence can be a result of a 'slip' or a 'lapse', where a slip is an outcome of lack of attention (e.g. taking the wrong dose, taking the wrong pill, etc.), and lapse, a "failure of memory" (e.g. forgetting to take a dose, forgetting that a dose has already been taken, etc.).[63] Intentional non-adherence can be a result of a 'mistake' or 'violation'. Mistakes are *correct* actions that have gone awry. They are further

separated into ‘rule-based mistakes’, and ‘knowledge-based mistakes’. Rule-based mistakes occur when a patient either incorrectly applies a good rule, or correctly applies a bad rule to tackle a particular scenario (e.g. stopping treatment with a non-addictive drug due to the fear of the possibility of getting addicted to it). Knowledge-based mistakes occur when no pre-existing rule applies to the situation at hand, and the patient must apply his/her knowledge (e.g. rather than getting a prescription refill immediately after a prior fill runs out unexpectedly, the patient decides against this being an emergency and delays this task).[63] Violations, on the other hand, are “deliberate deviations from safe practice” (e.g. choosing not to pick up a prescription as the patient feels that the physician did not pay heed to his/her comments, not following the dosage regimen directed by the physician and taking all medications together rather than at separate times, etc.).[63]

Arguing against the use of this binary categorization of non-adherence, Unni and Farris developed the Medication Adherence Reasons Scale (MAR-Scale).[73,74] They suggest that the intentional-unintentional classification limits the ability to identify specific reasons for non-adherence.[74] In the recently modified version of their scale, they categorized the reasons for non-adherence as having four factors – practicality issues (e.g. not being able to open the container, pharmacy being out of medicine, etc.), lack of necessity belief issues (e.g. perceived need for medication, perceived effectiveness of medication, etc.), forgetfulness issues, and concern belief issues (e.g. possible side-effects or long-term effects). This classification was developed based on the Anderson’s Behavioral Model[75], Leventhal et al.’s Common-Sense Model[76,77], and the data collected in their study[73]. The items in the MAR-Scale were based on the conclusions reached by a systematic review conducted by Vik et al.[10], and other studies pertaining to medication non-adherence.[78–82]

Estimation of health care quality. The Pharmacy Quality Alliance (PQA) considers medication adherence as an essential component of medication-use quality.[83] They recommend the use of proportion of days covered (PDC) to measure medication adherence. Specifically, they recommend calculation of medication adherence for seven therapeutic classes outlined by the National Committee for Quality Assurance (NCQA) – beta-blockers (BBs), angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs), biguanides, sulfonylureas, thiazolidinediones, and statins.[84] PDCs are also used by the Centers for Medicare & Medicaid Services (CMS). Their current guidelines use measures of medication adherence to determine bonus payments to capitated medicare advantage plans.[85]

The problem with PDCs is that they can only be calculated on retrospective data. Considering their importance, it is necessary to develop a scale that can provide a self-reported estimate of the PDC. Such a scale may help health care practitioners assess the quality of care being provided prior to the analysis of retrospective prescription fill data. Our literature review did not identify any disease non-specific self-reported measures of medication non-adherence that have been tested to estimate concurrent PDCs.

Thus, there is a need for a psychometrically-sound, self-reported measure of medication non-adherence, which is disease non-specific, theory-based, capable of distinguishing between the different reasons for non-adherence, and provides an estimate of the PDC measure.

Measurement of Medication Persistence and Need for a Self-Reported Instrument

Medication persistence is usually operationalized as the duration of time from initiation to discontinuation of therapy, after accounting for therapeutically permissible gaps.[3,23,28,84,86] This requires the use of prescription claims, pharmacy refill, pill counts, or clinical trials data.[3,23,87,88]

According to our review of the literature, currently, there are no multi-item self-reported measures of medication persistence in the scientific literature or health care practice that have been validated and tested for their reliability. But due to numerous issues with stopping pharmacotherapy without the consent of a health care provider, it is necessary to develop an instrument that can help identify patients who have been non-persistent with their medications, and the reasons behind such behavior.[5,23] Thus, the development of such a self-reported measure is pertinent.

Predicting Future Medication Adherence

Along with the assessment of concurrent medication adherence, estimating future non-adherence behavior is often of value to health care practitioners and researchers alike. Several self-reported instruments have been developed to aid in the identification of patients who have a higher propensity of being non-adherent to prescription medications.[89–114] The authors identified five measures that have been developed for, or validated in, multiple chronic diseases – the Adherence 14 (A14) scale[93], the Adherence Starts and Knowledge-20 (ASK-20) scale[99], the Medical Adherence Measure (MAM)[106], the Beliefs and Behaviour Questionnaire (BBQ)[111], and the Adherence Estimator (AE)[112–114]. Out of these, only the AE has been tested for its predictive validity using prospective pharmacy claims data.[113] The AE is a 3-item instrument used to assess "proximal beliefs related to intentional non-adherence."[113] These items assess the patients' perceived importance of their prescription medication(s), worries about potential side/adverse effects, and perceived financial burden. This instrument has presented good psychometric properties and has been shown to successfully predict future medication non-adherence.[112–114] However, due to its focus on intentional medication non-adherence, the prediction of potential

unintentional medication non-adherence is left unaddressed. Thus, development of a scale that can predict a wider scope of future non-adherence behaviors is necessary.

SPECIFIC AIMS

As mentioned in the prior section, medication non-adherence and non-persistence are important issues in health care.[1,2,4–7] Despite this, there are numerous gaps in the measurement of these constructs.[12] This dissertation sets forth the following specific aims to bridge such gaps in the literature:

Paper 1: To develop two self-reported measures – the Medication Non-Adherence Scale (MNAS) and the Medication Non-Persistence Scale (MNPS)

- The MNAS will be a health care practice setting administrable, disease non-specific measure of medication non-adherence with the ability to distinguish between the different reasons for non-adherence, and provide a self-reported estimate of the proportion of days covered (PDC) measure[23,26–29]
- The MNPS will be a health care practice setting administrable, disease non-specific measure of medication non-persistence.

Paper 2: To test the ability of the MNAS in predicting objectively measured *future* medication non-adherence (i.e., using PDCs)

Paper 3: To compare the abilities of the MNAS and other relevant scales in predicting objectively measured medication non-adherence; specifically:

- To compare the ability of the MNAS, the 1986 Morisky scale, and the MAR-Scale in predicting objectively measured *concurrent* medication non-adherence (i.e., using PDC)

- To compare the ability of the MNAS and the Adherence Estimator®[xi] in predicting objectively measure*d future* medication non-adherence (i.e., using PDC)[27,112–115]

SIGNIFICANCE

Medication Non-Adherence Scale (MNAS)

This dissertation is concerned with the development of two self-reported measures, the first of which is the Medication Non-adherence Scale (MNAS). This scale was designed to offer the following properties:

- Health care practice setting administrable
- Disease non-specific
- Ability to distinguish between the different reasons for non-adherence
- Provide a self-reported estimate of the proportion of days covered (PDC) measure
- Predict future medication non-adherence

Although, as discussed in earlier sections, many of the current self-reported scales possess some of the properties mentioned above, our literature review did not reveal any measure that bore all of these properties. Thus such a scale may offer multiple benefits to health care practitioners and researchers.

Medication Non-Persistence Scale (MNPS)

This dissertation is also concerned with the development of the Medication Non-Persistence Scale (MNPS). As addressed earlier, this will be the first multi-item self-reported measure of medication persistence in contemporary scientific literature. Development of the

MNPS may offer health care practitioner and researchers a much needed insight into the reasons behind medication non-persistence.

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[*] The literature refers to four terms in the area of medication-taking behaviors – adherence, compliance, persistence, and concordance.[1–3] One is often confused for the other. Concordance, a term more prominent in the United Kingdom, is used to denote a "therapeutic alliance" between the health care practitioner and the patient.[1,116] It embodies the epitome of contemporary patient-centered care. Although often classified as a medication-taking behavior, Horne and colleagues state that it paints a more normative picture.[2] Persistence refers to taking ones medications long-term, continually.[88] It is also defined as the amount of time that a patient follows the prescribed treatment regimen.[3] If a patient follows the prescribed therapy (after accounting for therapeutically permissible gaps), he/she is said to be persistent. Adherence and compliance are often used interchangeably. There are however, subtle differences. Compliance assumes that the patient is merely, and passively, following the health care practitioner's "orders", while adherence considers the patient in a more active role (takes medication, follows diet, brings about lifestyle changes, etc.).[1,2,117] In today's world of patient-centered care, the term 'adherence' is generally preferred by health care practitioners as 'compliance' may suggest oppression or order-following.[1,9] Thus in this dissertation, the term 'adherence' will be used to depict this type of medication-taking behavior.

[†] Two types of classifications of methods for measuring medication adherence are most commonly found in the literature – direct versus indirect[9,11], and objective versus subjective[10]. Direct methods purport to measure actual medication adherence (e.g. by direct patient observation, or biological assays and biomarkers), and are said provide "proof" of adherence[11], while indirect measures use surrogates such as prescriptions filled, opening of prescription bottle cap, pills remaining, etc.[9] Self-reported measures are considered to be subjective measures, while all other methods discussed here are considered to be objective. This distinction has been made on the premise that responses to self-reported measures may be affected by issues like social desirability bias[118], making them more 'subjective'.[10]

[‡] As emphasized by Garfield and colleagues in their recent review, when the purpose of the instrument is administration in a clinical setting, the length of the instrument is important.[12] Thus, shorter the instrument, lesser the time spent by the health care practitioner on adherence assessment.

[§] A point to note here is that the use of the term 'adherence' (or 'non-adherence') implies that the patient plays a more active role in medication-taking behavior. It is this assumption of an active role that enables the possibility of intentional medication non-adherence. If a patient were assumed to play a passive role in medication-taking (i.e. along the lines of 'compliance'), the distinction between the intentionality of such behavior would have been virtually impossible [67,68].

[**] Contrary to this, Unni and Farris[119] concluded that in the case of Medicare enrollees, "concern beliefs" in medications were a significant predictor of unintentional non-adherence. Their operationalization of unintentional non-adherence was based on the 1986 Morisky scale. They recommend that this finding demands further study.

[††] For the 1986 Morisky scale: two items are used to represent intentional non-adherence ("When you feel better do you sometimes stop taking your medicine?", "Sometimes if you feel worse when you take the medicine, do you stop taking it?"), and two for unintentional non-adherence ("Do you ever forget to take your medicine?", "Are you careless at times about taking your medicine?") [50].

[‡‡] For the RAM: the item used to measure intentional non-adherence is: "Some people […] say that they miss out a dose of their medication or adjust it to suit their own needs. How often do you do this?" While the item used to measure unintentional non-adherence is: "Some people forget to take their medicine. How often does this happen to you?"

[§§] This framework has also been called the 'accident causation framework' and the 'human error theory'.[12,63,64]

[***] Barber named his adaptation of the model, 'medical error theory'.

[†††] 'Non-adherence' has been termed 'non-compliance' in Barber's 2002 adaptation of the model of accident causation, but based on Lehane and McCarthy's arguments, and to be consistent with the rest of this research proposal, we will continue referring to this medication-taking behavior as non-adherence.[63,67,68]

[xi] Adherence Estimator is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA. US and non-US Patents Pending.

CHAPTER II:
PAPER 1
DEVELOPMENT OF THE MEDICATION NON-ADHERENCE SCALE (MNAS) AND THE MEDICATION NON-PERSISTENCE SCALE (MNPS)

In preparation for *Medical Care*

Format adapted for dissertation

ABSTRACT

Background

Although there are numerous self-reported measures of medication non-adherence in the scientific literature, no single measure has demonstrated evidence of having good psychometric properties, being disease non-specific, distinguishing between the different reasons for non-adherence, and offering an estimate of the proportion of days covered (PDC) measure. Also, there is no multi-item self-reported measure of medication non-persistence in the scientific literature or health care practice.

Objectives

To develop two self-reported measures – the Medication Non-Adherence Scale (MNAS) and the Medication Non-Persistence Scale (MNPS)

Research Design

A cross-sectional survey containing the MNAS and the MNPS was administered to patrons of three independent community pharmacies. The patients' survey responses were linked with their prescription fill data to study the internal consistency reliability, and convergent, discriminant and concurrent validity of the scales being developed.

Subjects

A total of 685 patrons of three independent community pharmacies located in the Southeastern region of the US were included in the sample for analysis involving the MNAS, and 675 for analysis involving the MNPS.

Measures

The MNAS assessed the extent and reasons for non-adherence, and the MNPS assessed the reasons for non-persistence. PDC was used as the criterion measure of validating the MNAS, while 'days to discontinuation' performed this function in the case of the MNPS.

Results

The MNAS presented with a five factor solution – Intentional non-adherence due to worries about side-effects, intentional non-adherence due to worries about addiction to the medication, intentional non-adherence due to worries about cost of the medication, intentional non-adherence due to lack of perceived need of the medication, and unintentional non-adherence. The MNPS yielded a single factor solution. Both scales demonstrated strong evidence of internal consistency reliability (all Cronbach's α values and composite reliabilities were greater than 0.7), and convergent (all standardized factor loadings were greater than 0.5 and significant, and no evidence of cross-loadings was observed), discriminant (all chi-square difference values were above the critical value, and all average variance extracted values were at acceptable levels) and concurrent validity (relationships between the MNAS and PDC (unstandardized regression coefficient = -0.50 ($p < 0.01$)), and MNPS and days to discontinuation (unstandardized regression coefficient = -3.97 ($p = 0.03$)) were statistically significant and in the expected direction). Based on a ROC curve analysis of the MNAS, individuals who score more than '16'

on the scale were considered non-adherent. Individuals who score more than ‘0’ on the MNPS were considered non-persistent.

Conclusions

The Medication Non-Adherence Scale (MNAS) and the Medication Non-Persistence Scale (MNPS) demonstrated good psychometric properties. They have been designed to help fill crucial gaps in relevant literature and health care practice. If used in a health care practice setting, these scales may help identify reasons behind such behavior, and aid in the development of tailored interventions to improve patient health.

INTRODUCTION

Medication non-adherence occurs when a patient misses, skips, delays, or takes more/less of the dose of the prescribed medication regimen.[1–5] Medication non-persistence refers to stopping or discontinuation of the treatment regimen.[4,6] Such behaviors are important issues in health care.[1,2,7–10] Many studies conducted in chronic conditions such as diabetes mellitus, hypertension, hypercholesterolemia, and congestive heart failure have demonstrated the detrimental effects of medication non-adherence and non-persistence on hospitalizations, mortality, and resultant overall health care costs.[8–10] Due to these reasons, effective and efficient measurement of medication non-adherence and medication non-persistence is necessary.

There are numerous methods of measuring medication non-adherence in the scientific literature and healthcare practice. Broadly, these may be divided into 'objective methods' and 'subjective methods'.[11] Objective methods include biological assays, pill counts, use of the electronic devices (e.g. Medication Events Monitoring System (MEMS)), pharmacy records and prescriptions claims, etc., while subjective methods include patient interviews, patient diaries and self-reported questionnaires. Despite the abundance of methods, no measure is universally agreed upon as a 'gold standard'.[5,11–18] As each of these instruments measure the construct differently, recent papers suggest that rather than anointing a measure as a gold standard, the choice of measurement should depend on the demands of the situation.[14] In a health care practice setting, which is the focus of the current study, self-reported questionnaires may be the only

pertinent tool to measure medication non-adherence. This argument is supported by the National Collaborating Centre for Primary Care and the Royal College of General Practitioners (London, UK), along with National Institute of Health and Clinical Excellence (NICE), and corroborated by Garfield and colleagues.[14,19]

There are many self-reported instruments available for measuring medication non-adherence – 1986 Morisky scale[20], Medication Adherence Reasons Scale (MAR-Scale)[21], Medication Adherence Rating Scale (MARS)[22], Brief Medication Questionnaire (BMQ)[23], Maastricht Utrecht Adherence in Hypertension (MUAH)[24], Brief Adherence Rating Scale (BARS)[25], Morisky Medication Adherence Scale[26], etc. Currently, the most widely used self-reported measure in a clinical setting is the 1986 Morisky scale.[20] The primary reason for its popularity is its short length and its ability to be used as a disease non-specific instrument.[27–31]. Despite these advantages, it has often presented issues with psychometric properties.[20,27,28,30–32] The Morisky scale was updated in 2009 to improve upon its reliability, but this version has twice the number of items (as compared to the 1986 version), and has only been tested among hypertensive and diabetic patients.[26,33–36]

Another shortcoming of many current instruments is that they often do not explicitly distinguish between the different reasons for medication non-adherence.[14,37] Some scientific papers propose distinguishing the reasons for non-adherence based on intent, into intentional and unintentional non-adherence.[14,38,39] Intentional medication non-adherence occurs when a patient makes a conscious decision to not comply with the medication regimen (e.g. stopping medication due to side- or adverse-effects, perceived lack of need, unaffordability, etc.). Unintentional medication non-adherence occurs when a patient simply forgets to take his/her medication(s). In their recent paper on the development of the Medication Adherence Reasons Scale (MAR-

Scale), Unni and Farris stressed on the importance of further distinguishing between the different reasons for *intentional* non-adherence. They observed that non-adherence can occur due to four issues – practicality issues (e.g. not being able to open the container, pharmacy being out of medicine, etc.), lack of necessity belief issues (e.g. perceived need for medication, perceived effectiveness of medication, etc.), concern belief issues (e.g. possible side-effects or long-term effects), and forgetfulness issues. Irrespective of the depth of classification implemented, the necessity of distinguishing between the different reasons for medication non-adherence is unhindered because the interventions needed to counter each type are quite different.[14,37] For example, reminder phone calls, SMSs, emails, etc. may work while intervening upon unintentional medication non-adherence or forgetfulness issues, while counseling may be necessary for dealing with intentional medication non-adherence or any of the other three issues mentioned in the MAR-Scale.

Medication persistence is usually measured using prescription claims data, pharmacy refill records, pill counts, or clinical trials data.[4,6,40,41] It is most often operationalized as the amount of time from initiation to discontinuation of the treatment regimen, or as a binary variable depicting whether the regimen was followed over the observation period or not.[4,6,40,42–44] Studies have indicated that behaviors such as stopping pharmacotherapy without the health care provider's consent may result in adverse health and/or economic issues.[9,10,40] Thus identification of patients who may have been non-persistent with their medications is important. Based on the recommendations by the National Collaborating Centre for Primary Care and the Royal College of General Practitioners (London, UK), and National Institute of Health and Clinical Excellence (NICE), this may be achieved by the use of self-reported measures.[19] But currently, health care

research and practice lacks multi-item self-reported measures of medication non-persistence. Such measures can also aid in the identification of reasons for non-persistence.

In order to address these gaps in current scientific literature, this paper proposes the development of the Medication Non-Adherence Scale (MNAS) and the Medication Non-Persistence Scale (MNPS). As discussed above, the MNPS is the first multi-item self-reported measure of medication non-persistence. Thus, its development is important to health care research and practice. But there are numerous self-reported measures of medication non-adherence in the scientific literature. The MNAS has been designed to offer five beneficial properties. First, it is designed to be disease non-specific. This will enable implementation of the MNAS in a variety of therapeutic areas. Second, the MNAS is grounded in theory. Conventional health behavior theories such as the social learning theory/social cognitive theory, theory of reasoned action/theory of planned behavior, health behavior model, transtheoretical model, etc. offer explanations for intentional medication non-adherence.[45–49] The model of accident causation promises to explain the intentional and unintentional aspects of this medication-taking behavior, and has been recommended as a conceptual framework for aiding in the operationalization of this distinction.[14,38,39,50,51] According to this model, unintentional medication non-adherence can be defined as a 'slip' (an outcome of lack of attention) or a 'lapse' (an outcome of forgetfulness), while intentional medication non-adherence can be defined as a 'mistake' (intentional implementation of an inappropriate action in a given scenario) or 'violation' (a deliberate implementation of an normatively unsafe action).[38] The MNAS is based on this model, and the suggestions offered by Unni and Farris[21,37] in their development of the Medication Adherence Reasons Scale (MAR-Scale). This ability to distinguish between the different reasons for medication non-adherence is the third advantage offered by the MNAS.

Fourth, it is developed using proportion of days covered (PDC) as the criterion measure. This objective measure is recommended for the measurement of medication adherence for use in the assessment of pharmacy quality by the Pharmacy Quality Alliance (PQA) and the Centers for Medicare and Medicaid Services.[52,53] Thus, the MNAS will offer self-reported estimates of the patients' PDCs to health care providers who choose to use it. Finally, the ultimate goal of this scale development exercise is to offer practitioners a relatively short, simple, and readily interpretable instrument to help assess medication non-adherence in a practice setting. Although other scales offer many of the properties discussed above, to the best of our knowledge, no scale offers all five. The MNAS has the potential of helping health care practitioners and researchers improve their assessment of medication non-adherence.

METHODOLOGY

Description of the Proposed Instruments

The Medication Non-Adherence Scale (MNAS) has been designed as a disease non-specific instrument with the ability to distinguish between the different reasons for medication non-adherence. The instrument is based on Barber's adaptation of the model of accident causation proposed by Reason[38,39,50,51], and the insight offered by Unni and Farris[21,37] in the development of the Medication Adherence Reasons Scale (MAR-Scale). The items were developed based on the 1986 Morisky scale[20], the Medication Adherence Scale (MAS)[54], the Morisky Medication Adherence Scale[26], the Medication Adherence Rating Scale (MARS)[22], the Reported Adherence to Medication (RAM) scale[55], and the guidance offered by Barber[38,39], Garfield et al.[14], and Unni and Farris[21,37]. All items were scored from '1' through '5'on a five point Likert-scale with options 'Never', 'Rarely', 'Sometimes', 'Often', and 'Always'. The final scale items can be viewed in the appendix.

Unlike the MNAS, which is theory-based, development of the MNPS was an exploratory endeavor. The MNPS items can be viewed in the appendix. The items were worded such that a binary (yes or no) response is obtained. Each pro-non-persistence response was coded as '1', while each pro-persistence response will be coded as '0'. These scores were summed to form one patient specific score for medication non-persistence. A summated score of '0' (zero)

represented perfect medication persistence, while anything higher indicated some form of non-persistence.

Pretests

Prior to conducting the study, the MNAS and the MNPS underwent two rounds of qualitative pretest evaluations (Pretest 1 and 2), and one round of quantitative pretest evaluation (Pretest 3). Pretest 1 was conducted among eight faculty members at a university in the Southeastern region of the United States with experience in self-reported scale development. The purpose of this pretest was "subjective validation" (i.e. face and content validity) of the scales.[56] It was conducted by distributing the then current versions of the MNAS and MNPS to the sample frame via email, and receiving feedback by the same medium. This feedback was evaluated, and appropriate suggestions were incorporated into the wording of the items. Pretest 2 was conducted among six staff members at the same university, who were users of prescription medications for chronic conditions. Its purpose was to assess sources of response error in the proposed instruments by conducting six cognitive interviews.[57–60] Based on the arguments presented by Beatty and Willis, a combination of 'think-aloud' and 'probing' techniques were used to help improve the scales.[57] Patients were recruited via email. Their responses were recorded using a digital voice recorder. They were offered a $10 gift card to an online store in exchange for their participation. The voice recordings were transcribed, and important points were marked for consideration. The MNAS was modified by adding two items pertaining to unintentional non-adherence, and one pertaining to intentional non-adherence. The MNPS was left unaltered.

Pretest 3 was conducted to empirically assess internal consistency reliability (Cronbach's alpha and composite reliability), and convergent and discriminant validity of the MNAS and

MNPS, and their potential to invoke a socially desirable response.[61–65] To achieve these aims, a cross-sectional, observational study was conducted by administering the scales as an internet-based survey to a convenience sample of full-time students, faculty, and staff at a university in the Southeastern region of the United States, who take at least one prescription medication indicated for a chronic condition. In order to help increase sample size, the patients were entered into a drawing to win one of ten $25 gift cards to an online store. This method yielded 214 usable responses. The instrument administered contained six sections – screener, the MNAS items, the MNPS items, socially desirable response bias assessment questions[65], demographic characteristics, and patient comments. Patients were screened based on the number of medications for chronic conditions prescribed; only patients that consumed at least one such medication were included in the study. Data collected were analyzed in SAS 9.3 (SAS Institute Inc., Cary, NC) and Mplus 7.2 (Muthén & Muthén, Los Angeles, CA, USA). For calculating internal consistency reliability, Cronbach's alphas were calculated using the 'CORR' procedure in SAS with the 'ALPHA' option[*], and composite reliability was calculated using the method described by Fornell and Larcker.[61,62] Further, convergent and discriminant validity of the measures was tested using the procedures outlined by Anderson and Gerbing, and Kline.[63,64] Details about these procedures can be found in the analysis section of the study below. These analyses resulted in a two factor solution for the MNAS – intentional non-adherence and unintentional non-adherence – and a one factor solution for the MNPS. Based on these results and the statements mentioned in the comments section of the survey, two items were added to the MNAS – "I missed a dose of my medication because I did not get it refilled before I ran out" and "I missed a dose of my medication because I forgot to take it with me". Also, the need-based items in the MNAS were reworded to exclude the "at that time" portion of the statements. The

MNPS was modified by adding an item – "I stopped taking my medication because the medication did not work". Potential for socially desirable response bias was tested using the method described by Steenkamp, de Jong, and Baumgartner.[65] No statistical evidence of such bias was observed.

Study

Following changes to the MNAS and MNPS based on the results of the pretests, the scales were administered to a sample of patients currently consuming medications for hypertension, diabetes, and dyslipidemia.[†]

Study objectives and study design. This study had the following objectives:

- To calculate internal consistency reliability of the MNAS and MNPS (using Cronbach's alpha, and composite reliability as instructed by Fornell and Larcker)[61,62]
- To study convergent and discriminant validity of the MNAS and MNPS using the methods outlined by Anderson and Gerbing, Kline, and Fornell and Larcker[62–64]
- To study the concurrent validity of the MNAS and MNPS using measures calculated using prescription fill data as their respective objective measures (an adaptation of the NCQA PDC measure[‡] and time to discontinuation, respectively)[4,40]
- To calculate sensitivity and specificity of the MNAS and MNPS by classifying their scores into meaningful categories using receiver-operating characteristic (ROC) curves[66,67]

A retrospective observational study was conducted to meet these objectives. Data for the MNAS and MNPS were collected from patrons of three independent community pharmacies in the Southeastern United States. Retrospective prescription fill data for these patrons were

obtained from the pharmacies under consideration, and the self-reported data were linked with it to meet the aforementioned objectives.

Sample design and data collection. The target population of the study was prescription medication users who have been directed by their health care provider to consume at least one prescription medication indicated for a chronic condition. After finalizing Data Use Agreements (DUAs) with three independent community pharmacies in the Southeastern region of the United States, prescription fill data were obtained for a 12-month period prior to the date of data request[§]. These data were used to identify the sample frame. In these data, patients were only referenced using a unique patient identifier (PTID). Patients, 18 years and older, were selected based on whether they filled at least one prescription for a medication in one of the seven therapeutic categories of interest specified by the National Committee for Quality Assurance (NCQA)[44], starting at least 6-months prior to the end of the data. These therapeutic categories included beta-blockers (BBs), angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs), biguanides, sulfonylureas, thiazolidinediones, and statins.[44] Only PTIDs that had prescription fills for at least one of the seven categories, and starting at least 6 months before the end of the data, with the last fill ending at least 90 days after the first started, were included in the sample frame. This resulted in a sample frame with 4,554 patients. The PTIDs in these data were then linked to patient names and addresses by an independent data manager. The involvement of the independent data manager ensured that the researchers did not have access to any patient identifiers in accordance with the Health Insurance Portability and Accountability Act (HIPAA).[68]

Survey instrument packets were then created for each patient in the sample frame. These packets included a cover letter from the patronized pharmacy informing the patients about the

study and the survey instrument (containing a screener for whether they used the pharmacy we obtained their data from for most of their medications, the MNAS, MNPS, and demographic questions) printed on a business reply mailer, and were enclosed in an envelope with the appropriate name and address printed on a label on top. Each survey instrument contained a unique mailing identifier (MID) that was patient specific, and linked to the PTID. A matching MID was also printed on the address label to ensure that the survey instrument reached the correct patient. The MID was linked to the PTID by the researchers, and the PTID was linked to the patients' names and addresses by the independent data manager; neither had access to the other's crosswalk files. This method of using a second-level ID (rather than using the PTID for mailing) was implemented to further ensure that patients' identities were not exposed. The packets were then mailed via the United States Postal Service. Recipients were expected to complete the instrument and mail it back using the business reply mailer.

Data management. Data collected using the survey instrument were manually entered into a Microsoft Excel file. These data were then cleaned to eliminate patients who did not responded to items on the MNAS and MNPS (or provided invalid responses) and did not use the pharmacy we obtained their data from for most of their medications. The dataset was then converted into a SAS dataset and merged with the prescription fill data using the MID and PTID. This resulted in a single patient-fill level file. This file was further aggregated into a patient-therapeutic category level file. Each patient was assigned their own observation period based on the date of survey return postmark. For calculating the adaptation of the NCQA PDC measure, the observation period ranged from 7 months prior to the date of survey return postmark to 1 month after, while the measurement period ranged from the start of the first prescription fill 6 months prior to the date of survey return postmark to the end of the last prescription fill on or before that date (i.e.

date of survey return postmark). A 6-month measurement period was chosen based on the recall period for the MNAS. A 30-day period prior to the start of the measurement period was observed (pre-measurement period) to account for potential prescription fill overlaps from that period, and a 30-day period was observed after the end of the last fill in the measurement period (post-measurement period) to distinguish between potential discontinuation (i.e. absence of a prescription fill/refill for the therapeutic category under consideration in the post-measurement period) and potential non-adherence (i.e. presence of a prescription fill/refill for the therapeutic category under consideration in the post-measurement period). If potential non-adherence was observed, the measurement period was altered to end on the date of survey return postmark (even if the "last prescription fill" ended before this date). Data within the measurement period were used to calculate PDCs using the following formula[42,69–71]:

$$\text{PDC} = \frac{\text{Number of days the patient is covered by the drug in the measurement period}}{\text{Number of days in the measurement period}}$$

A days to discontinuation score was also calculated for each therapeutic category consumed. For this calculation, the observation period ranged from 13 months prior to the date of survey return postmark to 1 month after. The measurement period, in this case, ranged from the start of the first prescription fill 12 months prior to the date of survey return postmark to the end of the last prescription fill on or before that date (i.e. date of survey return postmark). A 12-month measurement period was chosen in concordance with the MNPS recall period. The days to discontinuation score was calculated by adding the days until a gap in medication therapy of 30 days or more was experienced by the patient.[42–44] The therapeutic category-specific PDCs and days to discontinuation scores thus obtained were then averaged to calculate patient-specific mean PDCs and days to discontinuation scores.[43] Further, the patient-specific mean days to discontinuation score was standardized by dividing by number of days in the patient's

measurement period and multiplying by 100. This was done to make the measure comparable across patients, as is in the case of PDCs. Thus the standardized patient-specific mean days to discontinuation score represented the number of days to discontinuation in a 100-day measurement period. Based on the NCQA guidelines for calculating PDCs, a minimum drug coverage of 90 days for MNAS validation, and 150 days for MNPS validation, was deemed appropriate.[44]

Data analysis. All analyses were conducted in SAS 9.4 and Mplus 7.3. Two confirmatory factor analyses (CFAs) were conducted. One CFA was conducted for MNAS in SAS 9.4 with maximum likelihood estimation, and the other for MNPS in Mplus 7.3 with robust weighted least square estimation (WLSMV – weighted least squares with mean and variance adjustment).[**] Final factor structures were established for the two scales using the results of additional exploratory factor analyses conducted on the Pretest 3 data as a guideline. The first aim of this study was to calculate internal consistency reliability. This was done using two methods. First, Cronbach's alphas were calculated for the sub-scales of MNAS, and MNPS using the CORR procedure in SAS 9.4 with the ALPHA option. Second, composite reliabilities (CR) were calculated for these scales using the method described by Fornell and Larcker.[62] This involves using the values obtained in the confirmatory factor analyses described above in the formula below:

$$CR = \frac{\text{Sum of standardized factor loadings squared}}{(\text{Sum of standardized factor loadings squared} + \text{Sum of standardized error terms})}$$

The second aim of this study was to test the convergent and discriminant validity of the MNAS and the MNPS. The results of the confirmatory factor analyses conducted for objective 1 were used to achieve this objective as well. To check for convergent validity, standardized factor loadings were observed to identify items with values below 0.5. Statistically nonsignificant

standardized factor loadings were then identified.[63] Further, modification indices (Lagrange Multiplier (LM) statistics) were inspected for evidence of potential cross-loadings (i.e., large values of LM statistics).[64]

Discriminant validity for the MNAS was assessed using the approach suggested by Anderson and Gerbing.[63] In this technique, the completely unconstrained model (in this case, the MNAS model on which the CFA was originally run) is referred to as the base model. The chi-square estimate for this model is noted. Then, covariance between each pair of factors is iteratively fixed at one, one at a time. At each iteration, the model is run, and the chi-square estimate is noted. If this difference between each such estimate and that of the base model is found to be greater than 3.84 (at $\alpha = 0.05$), we can say that there is evidence of discriminant validity between the corresponding pair of factors. In addition to these calculations, average variance extracted (AVE) was also calculated for the MNAS sub-scales, and the MNPS.[62] The formula for calculating AVE has been given below:

$$\text{AVE} = \frac{\text{Sum of squared standardized factor loadings}}{(\text{Sum of squared standardized factor loadings} + \text{Sum of standardized error terms})}$$

If an AVE value is observed to be greater than or equal to 0.5, or if it is lesser than 0.5 but is greater than its squared correlation with the other sub-scales/scale, we can say that there is evidence to suggest discriminant validity.[62]

The scores on items under each sub-scale were then summed to denote the score on that sub-scale. In order to study the concurrent validity of the MNAS, two multiple linear regressions were conducted. The first model contained the summated forms of the MNAS sub-scales as independent variables (i.e. each sub-scale as a separate IV), important demographic variables as covariates[††], and the patient-specific mean PDC measure as the dependent variable. The second model replaced the summated sub-scale scores in the prior model with a summated overall

MNAS score (i.e. only one IV). The SAS 9.4 GLM procedure was used for these analyses (using a significance level of 0.05).

Using a procedure similar to that outlined above, concurrently validity of the MNPS was studied against the standardized patient-specific days to discontinuation measure of persistence. A multiple linear regression was conducted using the summated MNPS score as the independent variable, important demographic variables as covariates[††], and the standardized patient-specific days to discontinuation score as the dependent variable. This was done using PROC GLM in SAS 9.4 (using a significance level of 0.05).

The last objective of this study was to classify the scores on the MNAS and the MNPS into meaningful categories. This was done to allow calculation of sensitivity and specificity of the scales, and more importantly, enable better interpretability in a health care practice setting. To do this, two receiver-operating characteristic (ROC) curves were plot, one for the MNAS, and another for the MNPS. This was done using the LOGISTIC procedure in SAS 9.4 with the PLOTS = ROC option. First, the patient-specific mean PDC and the patient-specific days to discontinuation (i.e. non-persistence) variables were converted into their categorical forms. In the case of PDC a 95% adherence criteria was used; individuals with a PDC of 95% or more were classified as 'adherent', while those with a PDC of less than 95% as 'non-adherent'.[‡‡] For the standardized days to discontinuation measure, individuals who had not discontinued any of their medications in the measurement period (i.e. when value on this measure was 100) were classified as 'persistent', while all others as 'non-persistent'. The ROC curve for MNAS were plot using the overall average MNAS score and the categorical patient-specific PDC variable. Similarly, the summated score on the MNPS, and the dichotomous standardized patient-specific days to discontinuation score were used to calculate the persistence ROC curve. These curves, and the

dataset generated from the LOGISTIC procedure (using the OUTROC option) were used to determine optimum cut-off points for the proposed scales.

RESULTS

Sample Description

After 40 days in the field, 831 completed responses were obtained, while 611 packets were returned by the USPS due to address issues. Thus, a response rate of 21.08% was observed (831 ÷ (4,554-611)). Following this, patients who either provided invalid responses to the MNAS or MNPS items, or did not use one of the three pharmacies under consideration for most of their medications for chronic conditions were eliminated. This resulted in the elimination of 124 patients. Furthermore, as mentioned in the prior section, different minimum drug coverage criteria were applied for MNAS (90 days) and MNPS (180 days) validation. Due to this, two separate patient-level files were created – the MNAS analysis file containing 685 patients, and the MNPS analysis file containing 675.

Table 1 provides information about the MNAS and MNPS sample characteristics. Considering the fact that patients were required to consume at least one medication for a chronic condition, and were administered a paper instrument (rather than online), the sample primarily comprised of middle-aged to old individuals. About 63% of the MNAS sample and about 60% of the MNPS sample was greater than 60 years of age. Considering that the number of medications prescribed usually increase with age, such an age distribution was deemed appropriate for the purposes of this study. The sample was also primarily white (87.3% for MNAS, 87.7% for MNPS), female (56.5% for MNAS, 56.9% for MNPS), and married (64.8% for MNAS, 65.3%

for MNPS). About 26% reported to having at least a college degree in either sample. Most patients (65.8% in both samples) were prescribed 3 to 8 medications for chronic conditions, with at least one of them being for diabetes, hypertension or dyslipidemia. Around 60% of either sample were either insured by Medicare, private insurance, or both, and most reported their health status as being 'good' (41.9% for MNAS, 39.9% for MNPS).

Confirmatory Factor Analysis, Internal Consistency Reliability, and Convergent and Discriminant Validity

Results of the confirmatory factor analysis for the MNAS can be viewed in Table 2.[§§] The analysis yielded a five factor solution – Intentional non-adherence due to worries about side-effects (MNAS-I-Side-effects – 4 items), intentional non-adherence due to worries about addiction to the medication (MNAS-I-Addiction – 2 items), intentional non-adherence due to worries about cost of the medication (MNAS-I-Cost – 2 items), intentional non-adherence due to lack of perceived need of the medication (MNAS-I-Perceived need – 4 items), and unintentional non-adherence (MNAS-U – 4 items). Confirmatory factor analysis results for the MNPS can be viewed in Table 3. This analysis yielded a single factor solution. The MNAS and MNPS items can be viewed in the appendix. Cronbach's α and composite reliability values for the MNAS sub-scales and MNPS can be viewed in Table 4. These values were greater than the recommended minimum of 0.7 on both measures.[61,62,72] Based on these results, we can say that we have sufficient evidence of internal consistency reliability for all sub-scales of MNAS and the MNPS.

Next, standardized factor loadings obtained in the CFA were observed to identify statistical nonsignificance and value below 0.5 (see Table 2 and 3). No such instance was

observed. After accounting for correlated errors in the MNAS model, all Lagrange Multiplier statistics were within limits, and no evidence of potential cross-loadings was observed. These findings indicated sufficient evidence of convergent validity.[63,64]

The method suggested by Anderson and Gerbing[63] and average variance extracted (AVE)[62] were used to assess discriminant validity in the MNAS, while only the latter was used for the MNPS. Using the prior approach for the MNAS, all chi-square differences observed were greater than 3.84 (critical value at $\alpha = 0.05$). The AVE value for all summated MNAS sub-scales scores, except unintentional non-adherence, was greater than 0.5. In the case of MNAS-U, AVE was observed to be 0.49. However, as this value was higher than the squared correlations of MNAS-U with the other sub-scales, all the MNAS sub-scales were concluded to demonstrate discriminant validity. AVE for the MNPS was computed to be 0.62, thus offering evidence for discriminant validity. The AVE values, correlation coefficients, and squared correlation coefficients can be viewed in Table 4.

Concurrent Validity

The MNAS sub-scale item scores were first summed, and then subjected to concurrent criterion validation using the patient-specific mean PDC. Based on the results of a set of univariable analyses conducted by regressing the patient-specific mean PDC on each measured demographic variable, the variable 'age' (measured in years) was included in the analysis as a covariate. First, the patient-specific mean PDC was regressed on the five MNAS sub-scale scores. This analysis indicated that the factor concerned with intentional non-adherence due to worries about medication costs (MNAS-I-Costs) was the only sub-scale that was statistically significantly associated with the patient-specific mean PDC (unstandardized regression

coefficient = -1.94 ($p < 0.01$)). Also, the relationship between patient-specific mean PDC and the factor concerned with intentional non-adherence due to a perceived lack of need of medication (MNAS-I-Perceived need) was marginally significant (unstandardized regression coefficient = -0.71 ($p = 0.08$)).*** A second linear regression model was run to assess the relationship between the summated overall MNAS score and patient-specific mean PDC. Result of this analysis indicated that there was a statistically significant relationship between the overall MNAS score and the patient-specific mean PDC (unstandardized regression coefficient = -0.50 ($p < 0.01$)). These results can be viewed in Table 5. Thus, based on this result, we can say that there is evidence to suggest that the MNAS has concurrent validity with the patient-specific mean PDC.

To assess concurrent validity of the MNPS, the scores on the items were summed to calculate one patient-specific MNPS score. Similar to the concurrently validation of the MNAS, a model building approach was used and the variable 'age' was included in the criterion validation analysis with the standardized patient-specific mean days to discontinuation score. The relationship between the MNPS score and the objective measure was not found to be statistically significant (unstandardized regression coefficient = -0.84 ($p = 0.21$)). As the development of the MNPS was an exploratory exercise, scoring on the MNPS was modified to enable better prediction of the objective measure; the summated MNPS variable was modified to a dichotomous variable with a value of '1' for patients with a score of '1' or more on the original MNPS (i.e. those who answered 'Yes' on at least one of the 9 items), and a value of '0' for patients with a score of '0' (i.e. those who did not answer 'Yes' on any item). After this modification, the MNPS was seen to demonstrate a statistically significant relationship with the standardized patient-specific mean days to discontinuation score (unstandardized regression coefficient = -3.97 ($p = 0.03$)). These results can be viewed in Table 6. Based on this result, we

can say that there is evidence to suggest that the MNPS has concurrent validity with the standardized patient-specific mean days to discontinuation score.

ROC Curve Analysis, Sensitivity, Specificity and Meaningful Categorization of Scale Scores

The ROC curve for MNAS presented a *c* statistic of 0.63. The dataset generated with the OUTROC option provided a range of predicted probabilities, sensitivity, and 1-specificity values. Using Youden's J[73] as a guideline, a cut-off point of 16.60 was obtained.††† At this point, the scale had a sensitivity of 0.74 and specificity of 0.45. To improve implementation of the MNAS in estimating PDC at a health care practice setting, because a score beyond 16 on the MNAS indicated that the patient selected a response other than 'Never' on at least one item, a cut-off point of 16 was deemed appropriate (a score beyond 16 indicates non-adherence), and thus finalized. At this point, the sensitivity was 0.81 and specificity was 0.30.

For the MNPS, the *c* statistic was observed to be 0.53 and the relationship between the original form of the scale and dichotomous standardized patient-specific days to discontinuation score was not statistically significant. Thus no further attempt was made to arrive at a cut-off point using this method. Rather, the dichotomous MNPS variable created in the concurrent validation process was considered to be the best representation of the scale for use in a health care practice setting, i.e. a score beyond 0 on the MNPS indicated non-persistence (as measured using the standardized patient-specific days to discontinuation score). However, this cut-off point yielded a sensitivity of only 0.24. The specificity value at this point was 0.82.

DISCUSSION

Numerous papers have demonstrated the ill-effects of non-adherence.[8–10] Yet based on our literature review, no self-reported adherence measure in health care practice has presented with good psychometric properties, is designed to be disease non-specific, and can help distinguish between the different reasons for non-adherence. This paper presents evidence for the Medication Non-Adherence Scale (MNAS) bearing those properties. Also, the ability of the MNAS in offering a self-reported estimate of the proportion of days covered (PDC) measure[40] is presented here.

There is also evidence to suggest that non-persistence results in a similar, if not worse, health and economic impact as non-adherence.[9,10] But the construct lacks a method of measurement that can offer health care practitioners an immediate estimate of their patients' relevant behaviors, and reasons for the same. This paper develops and presents evidence for one such measure – the Medication Non-Persistence Scale (MNPS).

Interpretation of Results and Recommendations for Use in a Practice Setting

A CFA of the MNAS yielded a five factor solution with four factors (worries about side-effects, worries about addiction to the medication, worries about cost of the medication, and lack of perceived need of the medication) concerned with intentional non-adherence, and one with unintentional non-adherence. The scale demonstrated good internal consistency reliability and

validity (convergent, discriminant, and concurrent). The concurrent validity analysis indicated that on average for every one unit increase in the overall MNAS score (higher score indicates a higher level of medication non-adherence), the adapted 6-month PDC measure dropped by 0.5 percentage points. Also, the ROC curve analysis indicated that a score of greater than 16 on the MNPS indicated a PDC of less than 95%. Thus if a patient presents with such a score on the MNAS, the sub-scales must be assess to identify reason(s) for non-adherence. This assessment can enable implementation of an appropriate medication adherence intervention strategy.

Results of the CFA conducted on the MNPS items indicated a single factor structure. This scale demonstrated good internal consistency reliability and validity (convergent, discriminant, and concurrent). Based on the analysis conducted during validation, a score of greater than '0' (zero) was deemed to indicate non-persistence, although this cut-off point presented with a low sensitivity value (0.24). Furthermore, individuals who indicated non-persistence on the MNPS were seen to stop medication consumption on average about four days before those who did not, in a 100-day period; i.e. on average about 15 days earlier in a one year period. If a patient presents with a score higher than '0' on the MNPS, their responses should be observed to identify the reason(s) for non-persistence, and an appropriate intervention strategy should be implemented.

Limitations of the Scales and Directions for the Future

Although this paper demonstrates strong evidence for reliability, validity, and applicability of the MNAS and MNPS, a few issues must be acknowledged before using these scales for research or in health care practice. The pretests and the study were conducted in three independent community pharmacies in the Southeastern region of the US, thus the authors

cannot make any claim about generalizability beyond this geographic area. Future studies need to test these scales in different geographic and socio-demographic samples to improve their external validity.

The MNAS and MNPS presented good statistical predictability of their objective counterparts, but the amount of variation explained in their respective criterion variables was observed to be quite low – 5.87% for MNAS and 1.32% for MNPS. Users of these scales must be cognizant of this shortcoming. The effect such an r^2 is seen in the poor specificity value of the MNAS (0.45). Such numbers potentially indicate an incomplete estimation of the objective measure. Although a thorough attempt was made by employing multiple rounds of qualitative and quantitative pretesting, future research should try and ensure that all aspects of the PDC construct are estimated by including additional factors for other reasons for non-adherence and non-persistence. One aspect of non-adherence that could be considered by future researchers is 'over-dosing'. The authors attempted to include items purporting to measure over-dosing in the MNAS, but they were removed due to model fit and cross-loading issues. An alternate explanation for this occurrence is the presence of socially desirable response bias. Although no statistical evidence was found for this bias in the pretests, it may have affected prediction in the study.‡‡‡ This hypothesis requires confirmation.

The work presented here does not study the comparative effectiveness of contemporary adherence scales in predicting PDC. Thus no claims can be made about the comparative performance of the MNAS. Future studies should assess the ability of other contemporary adherence scales like the 1986 Morisky scale[20], Medication Adherence Reasons Scale[21], etc. in predicting PDC, and compare results obtained using the MNAS.

Ideally, to develop better adherence interventions in a health care practice setting, having an estimate of the propensity for non-adherence in the future is more beneficial than an estimate of how a patient has behaved in the past. The Adherence Estimator® (AE)[74–76] is an example of a scale that has been developed for this purpose. The MNAS has not been tested for this ability. Future studies should assess the comparative predictive ability of the MNAS and the AE.

Conclusion

This paper outlined the development of two self-reported instruments that can be used to assess medication adherence and medication persistence in health care practice and research. The Medication Non-Adherence Scale (MNAS) was shown to distinguish between different reasons for non-adherence, and estimate concurrent and future medication non-adherence. It was tested in patients consuming medications indicated for diabetes, hypertension, and/or dyslipidemia, in a disease non-specific context. As indicated by a review of the literature, the Medication Non-Persistence Scale (MNPS) is the first multi-item self-reported measure of medication persistence. It was also tested in a similar disease non-specific context. Both scales were developed to enable relatively easy interpretation in a clinical setting, and allow health care practitioners to understand the reasons driving their patients' medication taking behavior.

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LIST OF APPENDICES

APPENDIX A

Table 1

Description of MNAS and MNPS sample demographic characteristics

Demographic Characteristics		MNAS		MNPS	
		#	%	#	%
Age	<= 45	43	6.3%	42	6.2%
	46 – 60	201	29.3%	200	29.6%
	61 – 70	196	28.6%	194	28.7%
	71 – 80	164	23.9%	161	23.9%
	> 80	81	11.8%	78	11.6%
Gender	Male	228	33.3%	226	33.5%
	Female	387	56.5%	384	56.9%
	Missing	70	10.2%	65	9.6%
Race	White	598	87.3%	592	87.7%
	Other races	84	12.3%	81	12.0%
	Missing	3	0.4%	2	0.3%
Education	Up to high school graduate	277	40.4%	275	40.7%
	Some college (no degree), trade or technical school, or associate degree	224	32.7%	222	32.9%
	Bachelors, professional, or graduate degree	178	26.0%	174	25.8%
	Missing	6	0.9%	4	0.6%
Marital Status	Married	444	64.8%	441	65.3%
	Currently not married	240	35.0%	234	34.7%
	Missing	1	0.1%	0	0.0%

Income	Under $20,000	167	24.4%	164	24.3%
	$20,000 to $39,999.99	166	24.2%	166	24.6%
	$40,000 to $59,999.99	95	13.9%	94	13.9%
	$60,000 to $79,999.99	64	9.3%	63	9.3%
	$80,000 or more	145	21.2%	143	21.2%
	Missing	48	7.0%	45	6.7%
No. of Medications	1 – 2	83	12.1%	83	12.3%
	3 – 4	170	24.8%	166	24.6%
	5 – 6	166	24.2%	164	24.3%
	7 – 8	115	16.8%	114	16.9%
	9 – 10	56	8.2%	55	8.1%
	> 10	72	10.5%	71	10.5%
	Missing	23	3.4%	22	3.3%
Health Insurance	Medicare	402	58.7%	393	58.2%
	Medicaid	74	10.8%	73	10.8%
	Private	435	63.5%	430	63.7%
	Uninsured	39	5.7%	39	5.8%
	Tricare	9	1.3%	8	1.2%
	Don’t know	7	1.0%	7	1.0%
	Missing	4	0.6%	3	0.4%
Health Status	Excellent	20	3.1%	20	3.0%
	Very Good	171	26.3%	169	25.0%

	Good	272	41.9%	269	39.9%
	Fair	180	27.7%	177	26.2%
	Poor	4	0.6%	39	5.8%
	Missing	2	0.3%	1	0.1%

APPENDIX B

Table 2

Confirmatory factor analysis results for the Medication Non-Adherence Scale

Constructs and Items[a]	Standardized Loading[b]
MNAS – Intentional – Side-effects	
I skipped a dose of my medication because I was worried about its side effects.	0.72
I skipped a dose of my medication because I was having side effects.	0.83
I took a smaller amount of my medication because I was worried about its side effects.	0.86
I took a smaller amount of my medication because I was having side effects.	0.79
MNAS – Intentional – Addiction	
I skipped a dose of my medication because I was worried about getting addicted to it.	0.94
I took a smaller amount of my medication because I was worried about getting addicted to it.	0.89
MNAS – Intentional – Cost	
I skipped a dose of my medication because I was worried about costs.	0.91
I took a smaller amount of my medication because I was worried about costs.	0.81
MNAS – Intentional – Perceived need	
I skipped a dose of my medication because I was feeling better.	0.77
I skipped a dose of my medication because I did not need it.	0.70
I took a smaller amount of my medication because I was feeling better.	0.80
I took a smaller amount of my medication because I did not need it.	0.72

Constructs and Items[a]	Standardized Loading[b]
MNAS – Unintentional	
I forgot to take a dose of my medication.	0.64
I missed a dose of my medication by mistake.	0.61
I missed a dose of my medication because I did not get it refilled before I ran out.	0.78
I missed a dose of my medication because I forgot to take it with me.	0.77
Overall Fit:	
χ^2 (and df)	273.47 (df = 87)
CFI	0.98
RMSEA (90% CI)	0.06 (0.05, 0.06)

[a] The model accounted for high error correlations (Lagrange Multiplier statistics).

[b] All standardized factor loadings were statistically significant at $\alpha = 0.001$.

APPENDIX C

Table 3

Confirmatory factor analysis results for the Medication Non-Persistence Scale

Constructs and Items	Standardized Loading[d]
I stopped taking my medication because I was worried about its side effects.	0.96
I stopped taking my medication because I was having side effects.	0.90
I stopped taking my medication because I was feeling better.	0.90
I stopped taking my medication because I was worried about getting addicted to it.	0.74
I stopped taking my medication because I did not need it anymore.	0.90
I stopped taking my medication because I did not want to take it.	0.76
I stopped taking my medication because it was inconvenient.	0.59
I stopped taking my medication because I was worried about costs.	0.58
I stopped taking my medication because the medication did not work.	0.68
Overall Fit:	
χ^2 (and df)	95.75 (df = 27)
CFI	0.96
RMSEA (90% CI)	0.06 (0.05, 0.07)

[d] All standardized factor loadings were statistically significant at $\alpha = 0.001$.

APPENDIX D

Table 4

Sub-scale means, standard deviations, Cronbach's α, correlations, composite reliability, and average variance extracted

		Mean	Std. Dev.	Cronbach's α	X1	X2	X3	X4	X5	X6
X1	**MNAS-I-Side Effects**	1.17	0.42	0.87	**0.88/0.64**	0.26	0.12	0.16	0.08	0.22
X2	**MNAS-I-Addiction**	1.11	0.40	0.91	0.51	**0.91/0.84**	0.12	0.21	0.08	0.19
X3	**MNAS-I-Cost**	1.25	0.60	0.85	0.35	0.34	**0.85/0.74**	0.12	0.20	0.12
X4	**MNAS-I-Perceived Need**	1.17	0.41	0.83	0.4	0.46	0.34	**0.84/0.56**	0.16	0.31
X5	**MNAS-U**	1.67	0.60	0.82	0.29	0.28	0.45	0.4	**0.79/0.49**	0.11
X6	**MNPS**	0.43	1.10	0.75	0.47	0.44	0.35	0.56	0.33	**0.94/0.62**

Note: Composite Reliabilities (CR) and Average Variance Extracted (AVE) are shown in **bold** on the Diagonal (CR/AVE). Correlations are shown on the lower matrix while squared correlations are shown on the upper matrix.

APPENDIX E

Table 5

Concurrent validation of the Medication Non-Adherence Scale

Dependent variable: Patients-specific mean PDC

Parameter	Estimate[c]	Std. Error	*p*-value
Model with MNAS sub-scale scores as independent variables (R^2 = 0.0587)			
Intercept	90.94	4.10	<0.01
MNAS-I-Side-effects	-0.16	0.40	0.69
MNAS-I-Addiction	0.85	0.86	0.32
MNAS-I-Cost	-1.94	0.54	< 0.01
MNAS-I-Need	-0.71	0.40	0.08
MNAS-U	-0.34	0.27	0.17
Model with overall MNAS score as independent variable (R^2 = 0.0453)			
Intercept	91.17	4.11	< 0.01
MNAS	-0.50	0.10	< 0.01

[c] The estimates have been adjusted for 'age'.

APPENDIX F

Table 6

Concurrent validation of the Medication Non-Persistence Scale

Dependent variable: Standardized patient-specific mean days to discontinuation

Parameter	Estimate[e]	Std. Error	*p*-value
Model with original MNPS score (R^2 = 0.0089)			
Intercept	85.32	3.95	<0.01
MNPS	-0.84	0.67	0.21
Model with dichotomous MNPS score (R^2 = 0.0132)			
Intercept	86.23	3.96	<0.01
MNPS-Dichotomous (non-persistent vs. persistent)	-3.97	1.86	0.03

[e] The estimates have been adjusted for 'age'.

APPENDIX G

Medication Non-Adherence Scale (MNAS)

Over the past SIX MONTHS, how often have you done the following things **without being advised to do so by your doctor**?

Please respond to all of the following statements by selecting **Never, Rarely, Sometimes, Often,** or **Always**.

	Never	**Rarely**	**Sometimes**	**Often**	**Always**
I forgot to take a dose of my medication.	○	○	○	○	○
I skipped a dose of my medication because I was worried about its side effects.	○	○	○	○	○
I skipped a dose of my medication because I was having side effects.	○	○	○	○	○
I skipped a dose of my medication because I was feeling better.	○	○	○	○	○
I skipped a dose of my medication because I was worried about getting addicted to it.	○	○	○	○	○
I skipped a dose of my medication because I did not need it.	○	○	○	○	○
I skipped a dose of my medication because I was worried about costs.	○	○	○	○	○
I took a smaller amount of my medication because I was worried about its side effects.	○	○	○	○	○
I took a smaller amount of my medication because I was having side effects.	○	○	○	○	○
I took a smaller amount of my medication because I was feeling better.	○	○	○	○	○
I took a smaller amount of my medication because I was worried about getting addicted to it.	○	○	○	○	○
I took a smaller amount of my medication because I did not need it.	○	○	○	○	○
I took a smaller amount of my medication because I was worried about costs.	○	○	○	○	○
I missed a dose of my medication by mistake.	○	○	○	○	○
I missed a dose of my medication because I did not get it refilled before I ran out.	○	○	○	○	○
I missed a dose of my medication because I forgot to take it with me.	○	○	○	○	○

APPENDIX H

Medication Non-Persistence Scale (MNPS)

Sometimes, people stop taking their medication. Have you done the following things in the **past ONE YEAR <u>without</u> being advised to do so by your doctor**? *Please circle your responses*.

I stopped taking my medication because I was worried about its side effects.	**Yes**	**No**
I stopped taking my medication because I was having side effects.	**Yes**	**No**
I stopped taking my medication because I was feeling better.	**Yes**	**No**
I stopped taking my medication because I was worried about getting addicted to it.	**Yes**	**No**
I stopped taking my medication because I did not need it anymore.	**Yes**	**No**
I stopped taking my medication because I did not want to take it.	**Yes**	**No**
I stopped taking my medication because it was inconvenient.	**Yes**	**No**
I stopped taking my medication because I was worried about costs.	**Yes**	**No**
I stopped taking my medication because the medication did not work.	**Yes**	**No**

[*] As the MNPS items are dichotomous, the Kuder-Richardson 20 reliability measure will be equivalent to the coefficient alpha.

[†] The National Committee for Quality Assurance (NCQA) recommends the calculation of proportion of days covered (PDC) for medications indicated for these three conditions. This measure is an essential component of the measurement of health care quality, and is used by CMS and some other payers to enhance reimbursement to providers.[53] As an adaptation of the NCQA PDC measure will be used as the criterion measure to validate the MNAS, the authors believe that limiting the study sample to these three conditions is justified.

[‡] The difference between the NCQA PDC measure and the adaptation used in this study was the length of the observation period – 12 months and 6 months, respectively. Due to this difference in observation period, the minimum drug coverage period used was also shorter – 150 days for the NCQA measure and 90 days of the adaptation.

[§] A month was assumed to be a 30 day period for this study.

[**] Due to the dichotomous nature of the MNPS items, a maximum likelihood estimation model was deemed inappropriate.

[††] Univariable linear regressions were conducted using each measured demographic variable as an independent variable and the patient-specific mean PDC (or the standardized patient-specific days to discontinuation measure) as the dependent variable. Variables that demonstrated statistically significant results were included in model as 'important demographic variables'.

[‡‡] A 95% criteria was chosen rather than the conventional 80% criteria[40,52,77] to enable better correspondence with the wording and scoring of MNAS items.

[§§] After looking at item distributions by using PROC UNIVARIATE in SAS 9.4, it was observed that most MNAS items had a skewed distribution. Thus, two methods were implemented to confirm the results of maximum likelihood estimation. First, the items were log transformed and estimated using maximum likelihood. Second, Mplus 7.3 was used to conduct a CFA with robust weighted least squares (WLSMV – weighted least squares with mean and variance adjustment).[78–80] Both methods yielded identical factor structures. Thus to enable calculation of a summated score by assuming that the items are linear, the model estimated using maximum likelihood was finalized.

[***] Most MNAS items and the patient-specific PDC measure had a skewed distribution. Thus, two methods were used to confirm the results of this regression. First, the patient-specific PDC measure was log transformed, and the model was re-run. Second, the model was re-run using PROC GENMOD with a log link and a Gamma distribution. Both methods yielded qualitatively identical results. The original ordinary least squares model was thus finalized to enable ease of interpretation of results.

[†††] This cut-off point was not decided based on the best Youden's J (which would also have offered a cut-off point of 17), but by assessing the top five J values and deciding in the favor of better sensitivity, rather than specificity. This decision was made because when estimating non-adherence, false positives (getting identified as non-adherent when actually adherent) are not as severe a problem as false negatives (getting identified as adherent when actually non-adherent).

[‡‡‡] The socially desirable response bias assessment questions were not included in the study as many Pretest 3 patients complained about the vague nature of those questions in the comments section. Upon finding no statistical evidence of such a bias in Pretest 3, the authors decided not to include those questions in the study to avoid any negative impact on the assessment of the non-adherence and non-persistence.

CHAPTER III:
PAPER 2
PREDICTIVE VALIDATION OF THE MEDICATION NON-ADHERENCE SCALE (MNAS)

In preparation for *Journal of the American Pharmacists Association*

Format adapted for dissertation

ABSTRACT

Objective

To assess the ability of the Medication Non-Adherence Scale (MNAS) in predicting future medication non-adherence.

Design

Prospective observational study

Setting

Three independent community pharmacies in the Southeastern United States.

Participants

Five hundred and seventy-nine patients, 18 years of age and older, who were prescribed at least one medication indicated for diabetes, hypertension, or dyslipidemia, and used one of the three pharmacies approached for most of their medications.

Main outcome measure

A 3-month adaptation of the National Committee for Quality Assurance (NCQA) proportion of days covered (PDC) measure.

Results

Three MNAS sub-scales – intentional non-adherence due to worries about medication cost (unstandardized regression coefficient = -1.17 (p = 0.02)), intentional non-adherence due to lack

of perceived need of the medication (unstandardized regression coefficient = -0.75 ($p < 0.05$)), and unintentional non-adherence (unstandardized regression coefficient = -0.65 ($p = 0.01$)) – were observed to be statistically significantly associated with future medication non-adherence. The overall summated version of the MNAS was also observed to estimate future PDC (unstandardized regression coefficient = -0.62 ($p < 0.005$)). Results of the ROC curve analysis demonstrated that a score beyond 20 on the MNAS may indicate incidence of medication non-adherence in the next three months.

Conclusion

This study demonstrated the ability of the MNAS in predicting medication non-adherence in the next three months after administration.

INTRODUCTION

Medication non-adherence is an important issue in health care.[1–6] Numerous studies have demonstrated its adverse effects on health care utilization in diseases such as myocardial infarction, diabetes mellitus, hypertension, hypercholesterolemia, and congestive heart failure.[2–4,6] Studies have also concluded that such behavior can lead to an increase in the cost of health care.[2,6] Recent estimates indicate that an additional $317.4 billion may be attributable to non-adherence.[2] Moreover, a report by Horne et al. concluded that 30 to 60% of medications are not consumed as prescribed.[5] Due to the expanse of this issue, numerous methods have been devised to measure the construct – direct patient observation, drug level in biological fluids / biological assays and biomarkers, pill counts, prescription refill records and administrative claims data, electronic monitoring, and self-report.[7–15]

Some researchers propose that among the methods listed above, electronic monitoring using MEMS should be considered a 'gold standard' measure.[15–17] But recent papers suggest that rather than anointing a gold standard, the choice of measure should depend on the measurement setting.[10] Due to their feasibility and practicality, self-reported measures appear to be the only pertinent tool to measure medication non-adherence in a clinical practice setting, which is the focus on the current paper. In accordance with this claim, the National Collaborating Centre for Primary Care and the Royal College of General Practitioners (London, UK), and the

National Institute of Health and Clinical Excellence (NICE) recommended the use of self-reports in this setting.[18]

There are numerous self-reported measures of medication adherence in use in health care research and practice today – 1986 Morisky scale[19], Medication Adherence Rating Scale (MARS)[20], Brief Medication Questionnaire (BMQ)[21], Brief Adherence Rating Scale (BARS)[22], Morisky Medication Adherence Scale[23], Medication Adherence Reasons Scale (MARS)[24], etc. These measures have been developed to assess concurrent or past medication adherence behavior. But oftentimes, prediction of future medication non-adherence behavior is equally important. If estimated effectively, this may enable the implementation of interventions prior to the potential occurrence of non-adherence, and may prevent its aforementioned negative impact.

Researchers have developed several instruments to help health care practitioners identify patients with a higher propensity of being non-adherent.[25–50] For such an instrument to be usable in a wide range of practice settings, it must be disease non-specific. A review of the literature revealed five scales that have been developed for, or validated in, multiple chronic conditions – the Adherence 14 (A14) scale[29], the Adherence Starts and Knowledge-20 (ASK-20) scale[35], the Medical Adherence Measure (MAM)[42], the Beliefs and Behaviour Questionnaire (BBQ)[47], and the Adherence Estimator® (AE)[48–50]. The primary requirement of an instrument purporting to assess patients' future medication non-adherence, is an acceptable level of predictive validity. Out of the five measures listed, the Adherence Estimator® (AE) is the only instrument that has been tested for its predictive validity using pharmacy claims data.[48–50] The instrument has presented good psychometric properties and has yielded favorable results related to predictive validity. It is a 3-item instrument, and these items measure patients' perceived importance of prescription medications, worries about potential side/adverse effects of the medications

consumed, and perceived financial burden. Thus, the AE assesses the patients' proximal beliefs about intentional non-adherence.[49]

Many researchers in recent years have stressed on the importance of distinguishing between different reasons for non-adherence.[10,24,51] These are broadly divided into intentional and unintentional medication non-adherence.[10,52–61] This distinction is important because the rationale for non-adherence is different in the case of its two forms. Thus, the methods needed to intervene and improve future adherence are different as well. Strategies to counter intentional non-adherence should focus on improving the patient-physician relationship, implementing techniques derived from health behavior models, etc., while reminder phone calls/text messages/emails, pills-boxes, etc. are more effective in the case of unintentional non-adherence.[10,52,59,60,62,63] Moreover, Unni and Farris found evidence for further segregation of intentional non-adherence into practicality issues, issues pertaining to a lack of perceived necessity, and concern belief issues.[51] Despite the AE's commendable psychometric performance and simplicity, the lack of an unintentional medication non-adherence component and some aspects of the intentional non-adherence component, limits its applicability in a practice setting. Thus, there is a need for a scale that can predict a larger spectrum of reasons for future medication non-adherence to aid in the implementation of appropriate strategies to improve patients' medication-taking behavior.

The Medication Non-Adherence Scale (MNAS) promises to offer these properties.[64] It has been designed as a clinical practice setting administrable and disease non-specific measure of medication non-adherence. The scale has been demonstrated to distinguish between five reasons for non-adherence – worries about side effects, worries about addiction to the medication, worries about cost of the medication, lack of perceived need of the medication, and unintentional

non-adherence. It has been concurrently validated against an adaptation of the National Committee for Quality Assurance (NCQA) proportion of days covered (PDC) measure[65], among patients prescribed medications indicated in diabetes, hypertension, and dyslipidemia. The MNAS is based on Barber's adaptation of Reason's model of accident causation[55,56,66,67], and the suggestions offered by Medication Adherence Reasons Scale (MAR-Scale) developed by Unni and Farris[24,51]. The items on the scales can be viewed in the appendix.

METHODOLOGY

Study Objectives and Study Design

A prospective observational study was conducted to test the ability of the Medication Non-Adherence Scale (MNAS) in predicting future medication non-adherence. Specifically, this study had two objectives:

- To assess the predictive validity of the MNAS using an adaptation of the NCQA PDC measure as an objective measure of future medication non-adherence.[14,65,68]
- To calculate sensitivity and specificity of the MNAS in predicting future medication non-adherence using receiver-operating characteristic (ROC) curves.[69,70]

Prescription fill data were obtained from three independent community pharmacy in the Southeastern region of the US. Patrons of these pharmacies, who were prescribed at least one medication indicated for diabetes, hypertension, or dyslipidemia were administered a survey containing the MNAS. The survey data were linked to the prescription fill data, and used to meet the aforementioned objectives.

Sample Design and Data Collection

Three independent community pharmacies in the Southeastern region of the United States were approached to participate in the study. Upon approval of Data Use Agreements (DUAs), the pharmacies were asked to provide prescription fill data for the past 7 months. These data were

used to identify the sample frame. Patients, identified only by a unique encrypted patient identifier (PTID), were selected based on whether they are 18 years of age or older, and filled at least one prescription for medications indicated for diabetes, hypertension, or dyslipidemia. Specifically, medications that fall under one of the seven therapeutic categories of interest specified by the National Committee for Quality Assurance (NCQA) were considered. These include beta-blockers (BBs), angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs), biguanides, sulfonylureas, thiazolidinediones, and statins.[65] Survey instrument packets, containing a cover letter from the pharmacy patronized and the survey instrument (with the MNAS and demographic questions), were created for each patient in the sample frame. An independent data manager linked the PTIDs to the patients' names and addresses, and printed address labels to be posted on the survey instrument packets. This was done to ensure that the researchers did not have access to the patients' identities. These packets were mailed to the patients, and they were expected to mail back the completed instrument via the business reply mailer enclosed.[*] Four months after the date of receipt of the last usable survey, the pharmacies were asked to provide an amendment to the participants' prescription fill data.[†]

Data Management

The survey data were linked to the prospective prescription fill data using PTID and an encrypted mailing ID (MID)[‡] as linking variables. The resultant patient-fill level file was then aggregated to a patient-therapeutic category level file. This file was used to calculate the proportion of days covered (PDC) measure for each therapeutic category of interest specified by the National Committee for Quality Assurance (NCQA)[65], using a 3-month prospective

prescription data measurement period. A 3-month period was used to improve the feasibility of the study. This 3-month period was patient specific, depending on, and starting from, the date of survey return postmark. The fourth month of prospective data were used to distinguish between potential non-adherence (i.e. if a prescription for a drug in the same therapeutic category is filled or refilled in this fourth month) and non-persistence (i.e. if such a fill or refill is not observed in this fourth month). Similarly, a 1-month period prior to the date of survey return postmark was observed to account for potential overlaps in fills or refills from that period. Based on the NCQA specifications, only participants that had drug coverage for a minimum of 60 days were included in this analysis. This file was further converted into a patient-level file, and the therapeutic category-specific PDCs were averaged to calculate patient-specific mean PDC scores. This file was used for data analysis.

Data Analysis

Data were analyzed using SAS 9.4. This study utilized the survey data collected in the study by Athavale et al, in their development of the MNAS.[64] Results of confirmatory factor analysis, and the subsequent internal consistency reliability, and convergent and discriminant validity analyses conducted using these data have been elaborately explained by the authors in their paper titled 'Development of the Medication Non-Adherence Scale (MNAS) and the Medication Non-Persistence Scale (MNPS)'[64]. In order to meet the first objective of this study – predictive validation of the MNAS – two multivariable linear regressions were conducted using the GLM procedure in SAS. In the first model, the summated MNAS sub-scales were used as independent variables, important demographic variables[§] as control variables, and the patient-

specific mean PDC variable as the dependent variable. In the second model, the MNAS sub-scale scores were replaced with the overall summated MNAS score.

To calculate sensitivity and specificity of the MNAS while predicting future medication non-adherence, the score on the scale was first divided into meaningful categories. This was done by constructing a receiver-operating characteristic (ROC) curve for the overall summated MNAS score. The patient-specific mean PDC variable was converted to a dichotomous adherence variable, assuming that patients with a score of 95% or above are adherent to their medications[**], and used in the ROC curve analysis. The optimum cut-off point thus determined was used to calculate sensitivity and specificity.

RESULTS

Sample Demographic Characteristics

The sample frame contained 4,554 patients. After 40 days in the field, 831 completed survey responses were obtained, and 611 packets were returned by the postal service due to incomplete or outdated mailing addresses. Thus, a response rate of 21.08% was observed. Upon joining this file with the prescription fill data, and creating a patient-level file by averaging the therapeutic category-specific PDCs, 579 patients remained in the final sample used for analysis.

Details about the sample used in this study can be viewed in Table 1. The inclusion criteria required the consumption of at least one prescription medication indicated for diabetes, hypertension, or dyslipidemia. Thus the average age of the sample was 65 years, and 64.1% of individuals were greater than 60 years of age. The sample was 57.3% female, 86.4% white, with 64.8% indicating that they were currently married. About 24% indicated that they were college educated. About half the sample indicated that they earned less than $40,000. About 65% of the sample indicated that they consumed 3-8 chronic medications, with at least one of them prescribed for diabetes, hypertension, or dyslipidemia. More than 50% of the sample were insured by Medicare, private insurance, or both, and about 90% indicated that they would classify their health status as from ‘very good’ to ‘fair’.

Predictive Validity of the MNAS

As described earlier, two multivariable regression models were conducted to assess the predictive validity of the MNAS. The results of both models can be viewed in Table 2. The first model contained the five MNAS sub-scale scores as independent variables. The results of this model identified a statistically significant association between three MNAS sub-scales and the adapted NCQA patient-specific mean PDC measure – intentional non-adherence due to worries about medication cost (unstandardized regression coefficient = -1.17 (p = 0.02)), intentional non-adherence due to lack of perceived need of the medication (unstandardized regression coefficient = -0.75 ($p < 0.05$)), and unintentional non-adherence (unstandardized regression coefficient = -0.65 (p = 0.01)). The regression estimates indicated that a higher score on the sub-scales was associated with a lower PDC value, which was the expected direction. The second regression model utilized an overall summated MNAS score rather than the sub-scale scores. This model found evidence for a statistically significant association between such a summated score and the adapted NCQA PDC measure (unstandardized regression coefficient = -0.62 ($p < 0.01$)). The results of these two models provided the necessary evidence to conclude that the MNAS has predictive validity with the adapted NCQA PDC measure.

Optimum Cut-off Point, Sensitivity, and Specificity

A ROC curve was plot using the LOGISTIC procedure in SAS 9.4 to arrive at an optimum cut-off point for the MNAS when estimating future medication non-adherence. A *c* statistic of 0.63 was obtained. The top five Youden's J values were assessed by comparing the resultant sensitivity, specificity, false positive, and false negative values generated. Considering that identifying a case of non-adherence (though at times incorrectly) is more important than

excluding adherent individuals, a decision was made to favor sensitivity over specificity, and a score of 20.7 on the overall summated MNAS was considered the optimal cut-off point. At this point, the scale had a sensitivity of 0.78 and specificity of 0.41. As the overall summated MNAS scale score can only be in the form of whole numbers, and for ease of interpretation in a practice setting, a cut-off point of 20 was finalized. At this point, the scale had a sensitivity of 0.72 and specificity of 0.48.

DISCUSSION

A review of the literature conducted by the authors identified five scales that were disease non-specific, and designed to offer an estimate of future medication non-adherence behavior – Adherence 14 (A14) scale[29], Adherence Starts and Knowledge-20 (ASK-20) scale[35], th Medical Adherence Measure (MAM)[42], Beliefs and Behaviour Questionnaire (BBQ)[47], and Adherence Estimator® (AE)[48–50]. But out of these, only the AE has been previously tested for its predictive validity.[48–50] Also, despite having favorable psychometric properties, the AE leaves a few reasons for non-adherence unmeasured. Due to such a limited spectrum of reasons, appropriate tailoring of interventions to improve medication adherence may be hampered.

The Medication Non-Adherence Scale (MNAS) has also demonstrated good psychometric properties, has been designed to be disease non-specific, and has been shown to distinguish between five reasons for non-adherence – intentional non-adherence due to worries about side-effects, intentional non-adherence due to worries about addiction to the medication, intentional non-adherence due to worries about cost of the medication, intentional non-adherence due to lack of perceived need for the medication, and unintentional non-adherence.[64] This paper provides evidence for the use of the MNAS as an instrument to predict future medication non-adherence. This scale has also been concurrently validated to estimate a 6-month measure of PDC.[14,64,65,68] Thus by demonstrating the ability of the MNAS in predicting both, concurrent and

future medication non-adherence, the evidence presented in this paper further improves the applicability of the scale in a practice setting.

Interpretation for Results and Recommendations for Use in Practice

Out of the MNAS sub-scales, those concerned with worries about medication cost, lack of perceived need, and unintentional non-adherence, were seen to have a statistically significant impact on future medication non-adherence. When the 3-month measure of future PDC was regressed on the overall summated MNAS, it was observed that on average, for every 1 unit increase in the MNAS score, the PDC percentage decreased by 0.61 percent. Further, the ROC curve analysis revealed that on average a score beyond 20 on the MNAS estimated a PDC below 95%. If a patient presents with such a score, his/her sub-scale responses must be considered to determine the type of intervention that is needed to improve medication adherence. Higher score on the unintentional non-adherence sub-scale will require reminders (SMS, email, phone call, etc.) to improve their adherence, while higher scores on the other sub-scales may require patient counselling to deal with the specific issue(s) at hand. If worries of medication cost is the primary driver of the overall summated MNAS score, either switching to cheaper generics, redirection to cost-saving programs from pharmaceutical companies, or patient counselling to improve the patient's understanding of the importance of medication may be necessary.

Limitations of the Scale and Directions for Future Research

The first limitation of the present study is the potentially low external validity of the results. This study was conducted among patrons of three independent community pharmacies in the Southeastern region of the United States. Though the results presented here depict a robust

association between the scale and the objective measure of medication non-adherence used, the authors cannot make any claims about its applicability in other geographic and demographic settings. Future studies must assess the applicability of this scale in other samples to improve its validity.

Athavale et al presented an elaborate account of pretests conducted to try and ensure the inclusion of all reasons for medication non-adherence.[64] They also noted the absence of any evidence of socially desirable response bias in the measure.[64] But the analysis conducted here indicates that the scale only explains 11.12% of the variation in future non-adherence. One reason for such a result may be found in the work published by Cole and colleagues.[71,72] They state that most psychological constructs are composed of three components – state, trait, and occasion. In testing whether past behavior can predict future behavior, the current paper may only have estimated the 'trait' component of medication adherence; the unexplained variation in future PDC may be estimated by appropriately extracting the 'state' and 'occasion' components of the construct. Future research should test such a hypothesis to improve the self-reported measurement of medication adherence.

Finally, though this study validates the MNAS using a generally accepted objective measure of medication adherence, it is necessary for future studies to comparatively assess the ability of other contemporary scales, particularly the Adherence Estimator® (AE)[49], in predicting future PDC. Such an assessment will help establish a superior scale for this purpose.

Conclusion

The Medication Non-Adherence Scale (MNAS) has been demonstrated to estimate concurrent[64] as well as future medication non-adherence, and distinguish between different

reasons for the same in a disease non-specific context[64]. On account of its validation against the proportion of days covered (PDC) measure of medication adherence, it may offer health care practitioners a tool for enhancing their reimbursement from payers.[††] Thus, the results elucidated by Athavale et al in their development of the MNAS[64] and those presented here, build a compelling argument for the use the MNAS in health care practice and research.

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LIST OF APPENDICES

APPENDIX A

Table 1

Description of sample demographic characteristics

Demographic Characteristics		#	%
Age	<= 45	34	5.9%
	46 – 60	174	30.1%
	61 – 70	172	29.7%
	71 – 80	136	23.5%
	> 80	63	10.9%
Gender	Male	190	32.8%
	Female	332	57.3%
	Missing	57	9.8%
Race	White	500	86.4%
	Other races	76	13.1%
	Missing	3	0.5%
Education	Up to high school graduate	240	41.5%
	Some college (no degree), trade or technical school, or associate degree	192	33.2%
	Bachelors, professional, or graduate degree	142	24.5%
	Missing	5	0.9%
Marital Status	Married	375	64.8%
	Currently not married	203	34.8%
	Missing	1	0.2%
Income	Under $20,000	150	25.9%

	$20,000 to $39,999.99	132	22.8%
	$40,000 to $59,999.99	82	14.2%
	$60,000 to $79,999.99	56	9.7%
	$80,000 or more	117	20.2%
	Missing	42	7.3%
No. of Medications	1 – 2	60	10.4%
	3 – 4	139	24.0%
	5 – 6	143	24.7%
	7 – 8	97	16.8%
	9 – 10	50	8.6%
	> 10	69	11.9%
	Missing	21	3.6%
Health Insurance	Medicare	339	50.2%
	Medicaid	66	9.8%
	Private	364	53.9%
	Uninsured	33	4.9%
	Tricare	6	0.9%
	Don’t know	6	0.9%
	Missing	4	0.6%
Health Status	Excellent	16	2.8%
	Very Good	137	23.7%
	Good	229	39.6%

	Fair	158	27.3%
	Poor	37	6.4%
	Missing	2	0.3%

APPENDIX B

Table 2

Predictive validation of the Medication Non-Adherence Scale

Dependent variable: Participants-specific mean PDC

Parameter	Estimate[c]	Std. Error	*p*-value
Model with MNAS sub-scale scores as independent variables (R^2 = 0.1112)			
Intercept	96.12	3.84	<0.01
MNAS-I-Side-effects	-0.53	0.39	0.18
MNAS-I-Addiction	0.50	0.81	0.54
MNAS-I-Cost	-1.17	0.50	0.02
MNAS-I-Need	-0.75	0.37	<0.05
MNAS-U	-0.65	0.25	0.01
Model with overall MNAS score as independent variable (R^2 = 0.1058)			
Intercept	96.16	3.82	<0.01
MNAS	-0.61	0.10	<0.01

[c] The estimates have been adjusted for age and race.

[*] This study uses the survey data collected in the paper by Athavale et al[64]. For a detailed explanation of the survey data collection methodology, please refer to their article titled 'Development of the Medication Non-Adherence Scale (MNAS) and the Medication Non-Persistence Scale (MNPS)'.

[†] Studies by Toy et al.[73] and Benner et al.[68] have assessed adherence at 3 months using PDCs. While Toy et al. concluded that in the case of a once-daily dose, the level of adherence does not change over time, Benner concluded that the PDC value decreases over time.

[‡] The MID was linked to the PTID, and was printed on each survey instrument. It was used to mask the survey responses from the independent data manager. The researchers possessed the crosswalk between the MID and the PTID, while the independent data manager possessed the crosswalk between the PTID and patients' names and addresses.

[§] A series of univariable linear regressions were conducted using the patient-specific mean PDC as the dependent variable and each measured demographic variable as an independent variable. Variables that demonstrated a statistically significant relationship with the DV were termed 'important demographic variables'.

[**] A cut-off point of 95% was used rather than the traditional 80%[68,74,75] based on the MNAS item wording.

[††] Proportion of days covered (PDC) is used by the Centers of Medicare & Medicaid (CMS)[76], and many private insurers to determine pharmacy use quality, which in turn is used to determine reimbursement.

CHAPTER IV:
PAPER 3
COMPARING THE MEDICATION NON-ADHERENCE SCALE (MNAS) WITH THE 1986 MORISKY SCALE, THE MEDICATION ADHERENCE REASONS SCALE, AND THE ADHERENCE ESTIMATOR®

In preparation for *Research in Social and Administrative Pharmacy*

Format adapted for dissertation

ABSTRACT

Background

There are numerous self-reported measures to estimate medication adherence. The Medication Non-Adherence Scale (MNAS) has offered promising results in estimating concurrent and future medication non-adherence.

Objective

To compare the ability of the MNAS, 1986 Morisky scale, and Medication Adherence Reasons Scale in estimating concurrent medication adherence, and the MNAS and Adherence Estimator® in estimating future medication adherence.

Methods

An observational study with retrospective and prospective phases was conducted among patrons of three independent community pharmacies in the Southeastern United States. A survey containing the scales to be assessed was administered to patients that have filled medications indicated for diabetes, hypertension, and/or dyslipidemia. The survey data were then linked to the patients' prescription fill data. Univariable linear regressions were conducted using each scale as the independent variable, and the appropriate proportion of days covered (PDC) variant (6-month retrospective or 3-month prospective) as the dependent variable. The statistical significance (at $\alpha = 0.05$), standardized regression coefficients, and R^2s were compared, and the

predicted values generated from each regression were used to assess whether the estimates generated by each scale are statistically significantly different from each other.

Results

In estimating concurrent PDC, the MNAS model generated an R^2 of 0.043, and a standardized regression coefficient of -0.208, the Morisky scale model generated an R^2 of 0.018, and a standardized regression coefficient of -0.134, and the MAR-Scale model generated an R^2 of 0.016, and a standardized regression coefficient of -0.125. In estimating future PDC, MNAS model generated an R^2 of 0.083, and a standardized regression coefficient of -0.288, the AE model generated an R^2 of 0.010, and a standardized regression coefficient of -0.099. Both relationships were found to be statistically significant. All estimates were also found to be statistically significantly different from those generated by the MNAS.

Conclusions

The MNAS was observed to perform better in estimating concurrent and future medication adherence than the comparator scales.

INTRODUCTION

The negative impact of medication non-adherence has been studied extensively. The resultant health-related and economic adverse effects have been demonstrated in a wide range of chronic diseases such as hypertension, diabetes, hypercholesterolemia, congestive heart failure, and myocardial infarction.[1–5] Numerous interventions have been devised to counter the issue of medication non-adherence.[6–13] But in order to implement a successful intervention, effective measurement of the construct is necessary.

A meta-analysis conducted by Peterson and colleagues concluded that most medication adherence interventions occurred in a practice setting.[8] According to the National Collaborating Centre for Primary Care and the Royal College of General Practitioners (London, UK), and the National Institute of Health and Clinical Excellence (NICE), self-reported questionnaires are best suited for measuring and identifying medication non-adherence in this setting.[14] This point is also supported by Garfield and colleagues at the British Medical Association.[15] A number of self-reported instruments have been developed over the past few decades to measure concurrent medication non-adherence, and predict the propensity of future non-adherence. These include the 1986 Morisky scale[16], Medication Adherence Reasons Scale (MAR-Scale)[17], Medication Adherence Rating Scale (MARS)[18], Brief Medication Questionnaire (BMQ)[19], Brief Adherence Rating Scale (BARS)[20], Morisky Medication Adherence Scale[21], Adherence 14 (A14) scale[22], Adherence Starts and Knowledge-20 (ASK-20) scale[23], Medical Adherence Measure (MAM)[24],

Beliefs and Behaviour Questionnaire (BBQ)[25], Adherence Estimator® (AE)[26–28] etc. Out of these measures, the 1986 Morisky scale is the most prevalent in measuring concurrent medication non-adherence in health care practice and research.[16,29–34] Its popularity is a result of its ability to be used across multiple chronic diseases. It has been used in diseases like diabetes, hypertension, HIV, fibromyalgia, cardiovascular diseases, etc.[29,30,32–34] Despite its prevalence, it has offered mixed results pertaining to internal consistency reliability.[16,29–33] Morisky et al. published an updated version of their scale in 2009 to overcome some of the downfalls of its predecessor.[21] But the 2009 Morisky scale (Morisky Medication Adherence Scale) has twice the number of items as the 1986 scale, and based on our literature review, has only been tested in the hypertensive and diabetic populations.[21,35–38]

Recently, Unni and Farris developed the Medication Adherence Reasons Scale (MAR-Scale) to help practitioners distinguish between the different reasons for non-adherence in the dyslipidemia and asthma.[17,39] This scale categorizes the reasons for non-adherence into four factors – practicality issues (e.g. not being able to open the container, pharmacy being out of medicine, etc.), lack of necessity belief issues (e.g. perceived need for medication, perceived effectiveness of medication, etc.), concern belief issues (e.g. possible side-effects or long-term effects), and forgetfulness issues. Though this scale has demonstrated respectable reliability and validity, it is seen to perform differently across disease conditions[17,39], and has only been validated against self-reported, "subjective" measures[17,40].

McHorney and colleagues developed the Adherence Estimator® (AE) in 2009.[28] It is a three-item scale designed to capture the proximal beliefs about intentional non-adherence.[28] The items measure perceived importance of medications, worries about adverse/side effects, and perceived financial burden. These items have been validated for identification of individuals who

have a propensity of being intentionally non-adherence to their medications in the future. The results have demonstrated a promising ability to predict future intentional non-adherence. In recent years, researchers have outlined the importance of assessing both, the intentional and unintentional, components of medication non-adherence.[15,34,41–49] The AE does not incorporate the unintentional component of medication non-adherence, and based on the MAR-Scale, also some aspects of the intentional component. It also has not been shown to yield valid, reliable, or meaningful results across multiple medications.[26,28]

The Medication Non-Adherence Scale (MNAS) is a self-reported measure of medication adherence which is designed to be practice setting administrable and disease non-specific.[50] Its ability to predict concurrent medication non-adherence has been tested in patients prescribed medications for diabetes, hypertension, and dyslipidemia.[50] It has presented with good psychometric properties, and can distinguish between five reasons for medication non-adherence – intentional non-adherence due to worries about side-effects, intentional non-adherence due to worries about addiction to the medication, intentional non-adherence due to worries about medication cost, intentional non-adherence due to lack of perceived need for the medication, and unintentional non-adherence.[50] There is also evidence to suggest that the MNAS can predict future medication non-adherence over a 3-month period.[51] Thus, the MNAS may help address some of the issues presented by the 1986 Morisky scale, the MAR-Scale, and the AE.

METHODOLOGY

Study Objectives and Study Design

A retrospective observational study was conducted among patrons of three independent community pharmacies in the Southeastern region of the United States to compare the Medication Non-Adherence Scale (MNAS) with the 1986 Morisky scale and the Medication Adherence Reasons Scale (MAR-Scale), and a prospective observational study was conducted to compare the MNAS with the Adherence Estimator®* (AE). The items on the MNAS can be viewed in the appendix. The 1986 Morisky scale was chosen as a comparator while measuring concurrent medication non-adherence, as it is the most widely used scale for this purpose.[16,29–34] The MAR-Scale was also chosen as a comparator while measuring concurrent medication non-adherence as it takes a similar approach for assessing the reasons for medication non-adherence as the MNAS, and has demonstrated good reliability and validity levels.[17,39] The AE was chosen as a comparator while measuring future medication non-adherence, as according to our review of the literature, it is the only disease non-specific scale that has been tested for its predictive validity against an objective measure.[22–28] Specifically, this study had the following objectives:

- To compare the ability of the MNAS and the 1986 Morisky scale in predicting objectively measured *concurrent* medication non-adherence (using an adaptation of the NCQA proportion of days covered (PDC) measure[52,53])

- To compare the ability of the MNAS and the Medication Adherence Reasons Scale in predicting objectively measured *concurrent* medication non-adherence (using an adaptation of the NCQA proportion of days covered (PDC) measure[52,53])
- To compare the ability of the MNAS and the Adherence Estimator® in predicting objectively measure*d future* medication non-adherence (using an adaptation of the NCQA proportion of days covered (PDC) measure[52,53])

Sample Design and Data Collection

Prescription fill data for the past one year were obtained from three community pharmacies in the Southeastern region of the US after Data Use Agreements (DUAs) were approved and signed. Patients that were 18 years or older, and were prescribed at least one medication indicated for diabetes, hypertension, or dyslipidemia were identified using an encrypted patient ID (PTID) assigned by an independent data manager[†]. The researchers specifically considered patients that started on one of seven therapeutic categories of interest specified by the National Committee for Quality Assurance (NCQA)[54] at least 6 months prior to the end of data. These therapeutic categories include beta-blockers (BBs), angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs), biguanides, sulfonylureas, thiazolidinediones, and statins.[54] The independent data manager then linked these PTIDs to patient names and addresses.

Survey instruments containing the MNAS, MNPS, a 5-point scale version of the 1986 Morisky Scale[17,39,55,56], the MAR-Scale[17], AE[28], and demographic questions, printed on a business reply mailers, were then printed for each patient in the sample frame. The survey instrument also contained a unique mailing ID (MID) assigned by the researchers, which was

patient specific, and linked to the PTID. The instrument was enclosed in an envelope with the appropriate name, address, and MID printed on it. The MID was used to mask the survey data from the independent data manager, and further protect patient privacy. After the receipt of completed surveys, the three pharmacies were asked to amend the prescription fill data to 4 months after the end of the survey data collection period.

Data Management

The survey data were manually entered into a Microsoft Excel file, and then linked to the prescription fill data using the MID and PTID such that there were 7 months of prescription fill data prior to the date of survey return post-marking (concurrent period), and 4 months after (predictive period).[‡] These periods were patient-specific as the date of survey return post-mark was different for each patient. Patients who did not respond to items on the MNAS, the 5-point scale version of the 1986 Morisky scale, the MAR-Scale, were eliminated from the concurrent period dataset. Those who did not respond to the MNAS and AE were eliminated from the predictive period dataset. The past 6 months of prescription fill data were used to calculate the proportion of days covered (PDC) measure for each of the seven therapeutic categories of interest.[52,57–59] A 6-month period was used in accordance with the recall period of the MNAS. PDCs were also calculated on the 3-month period after the date of survey return post-mark. Based on the NCQA guidelines for calculating PDCs, a minimum drug coverage of 90 days for the concurrent period, and 60 days for the predictive period, was deemed appropriate.[54] The therapeutic category-specific concurrent and predictive period PDCs were then averaged to calculate patient-specific mean concurrent and predictive period PDCs. As the number of patients that met the minimum drug coverage period was expected to differ for the two periods,

two separate analysis files were created, one for the concurrent period, and another for the predictive period.

Data Analysis

SAS 9.4 was used for data analysis. In order to compare the MNAS and the 5-point 1986 Morisky scale in predicting concurrent medication non-adherence, two linear regressions were conducted using the GLM procedure. The first model contained the overall summated MNAS score as the independent variable and the patient-specific mean concurrent period PDC as the dependent variable. The other model contained the adherence score obtained from the 5-point 1986 Morisky scale as the independent variable and the patient-specific mean concurrent period PDC as the dependent variable. Upon running these analyses, statistical significance (at α = 0.05), standardized regression coefficients, and R^2s obtained from the two models were compared. The predicted values from the two regression models were saved into a separate SAS dataset. The relative effectiveness of the two scales in predicting the patient-specific mean concurrent period PDC was then statistically compared using the saved predicted values via the procedure outlined by Steiger.[60,61] The MNAS and the MAR-Scale were compared in a manner identical to that mentioned above; the only difference being the replacement of the 5-point 1986 Morisky scale score with the score on the MAR-Scale.

The abilities of the MNAS and the Adherence Estimator® in predicting future medication non-adherence were then compared. For this, two linear regressions were conducted. The prior model included the overall MNAS score as independent variable and the patient-specific mean predictive period PDC as the dependent variable. The latter model included a categorical version of the score on the AE[§] as the independent variable and the patient-specific mean predictive

period PDC served as the dependent variable. The GLM procedure was used for these analyses. The ordered categories in the AE variable were treated quantitatively for this analysis. The two scales were then compared using the method explained in the preceding paragraph (i.e. while comparing the MNAS and the 5-point 1986 Morisky scale).

RESULTS

Sample Characteristics

The sample frame consisted of 4,554 patients. Survey instrument packets were created for each of these patients, and mailed. At the end of a 40 day data collection period, 831 completed responses were obtained. 611 packets were returned by the postal service due to improper addresses. Thus a 21.08% response rate was observed (831 ÷ (4,554-611)). After joining the prescription fill data to the data from the completed survey responses, the concurrent period file contained 666 patients, while the predictive period file contained 567.

The samples consisted of an older demographic with 64.1% (in both samples) reporting an age of greater than 60 years. About 30% of patients in either sample reported their age to be between 46 and 60 years. Both samples had a greater proportion of females (56.3% in the concurrent period sample and 57.3% in the predictive period sample), and about 87% reported their race as 'white'. Approximately 26% of the concurrent period sample and 24% of the predictive period sample reported having at least a bachelor's degree. About 65% in either sample reported their marital status as 'married', and about 48% reported an annual household income below $40,000. Approximately 65% of patients in both samples reported being prescribed 3-8 medications for chronic conditions. Most patients were privately insured (61.9% in the concurrent period and 53.1% in the predictive period), insured by Medicare (56.6% in the

concurrent period and 49.5% in the predictive period), or by both. About 40% of patients in either sample reported their general health status as being 'good'.

Comparison with the 1986 Morisky Scale

In order to compare the 1986 Morisky scale with the MNAS, two regression models were run. The MNAS model generated an R^2 of 0.04, and a standardized regression coefficient of -0.21 while the Morisky scale model generated an R^2 of 0.02, and a standardized regression coefficient of -0.13. Relationships between the scales and the patient-specific mean concurrent period PDC were found to be statistically significant at $\alpha = 0.05$. These results can be viewed in Table 2. The method proposed by Steiger[60] was implemented to statistically compare the relative effectiveness of the two scales in predicting the patient-specific mean concurrent period PDC. The results of this analysis indicated that there was a statistically significant difference in the relative effectiveness of the two scales ($p = 0.01$). Based on these results, the authors concluded that the MNAS is more effective in estimating concurrent PDCs than the 1986 Morisky scale.

Comparison with the Medication Adherence Reasons Scale

The MAR-Scale and the MNAS were compared using two regression models. The results of this comparison can be viewed in Table 2. The model with the overall summated MNAS score generated a higher R^2 value (0.04 versus 0.02 for the MAR-Scale) and a higher absolute value of the standardized regression coefficient (0.21 versus 0.12 for the MAR-Scale). Both relationships were found to be statistically significant at $\alpha = 0.05$. Further, the two scales were compared using the method outlined by Steiger.[60] The results of this analysis indicated that the comparative effectiveness of the two scales in predicting PDCs was statistically significantly different ($p =$

0.03). Thus, these analysis indicate that the MNAS is more effective in estimating PDCs than the MAR-Scale.

Comparison with the Adherence Estimator®

The MNAS was compared with the AE in predicting future medication non-adherence measured using an adaptation of the NCQA PDC algorithm. This was done using two linear regressions. The results of these regression models can be viewed in Table 2. The MNAS model generated an R^2 of 0.08, while the AE model generated an R^2 of 0.01.** The relationship between the overall summated MNAS score and the patient-specific mean predictive period PDC was found to be statistically significant with a standardized regression coefficient of -0.29. The relationship between the AE and the patient-specific mean predictive period PDC was also observed to be statistically significant (at $\alpha = 0.05$) with a standardized regression coefficient of -0.10. Also, when the effectiveness of the two scales in predicting PDCs was compared using the method proposed by Steiger[60], their predictive ability was statistically significantly different ($p < 0.01$). These analyses indicate that the MNAS is more effective in predicting patient-specific mean predictive period PDCs than the AE.

DISCUSSION

Medication non-adherence has been demonstrated to have detrimental health and economic effects in a variety of chronic diseases – hypertension, diabetes, hypercholesterolemia, congestive heart failure, and myocardial infarction.[1–5] Due to the awareness of this impact, numerous self-reported measured have been developed to estimate medication non-adherence, both concurrently and predictively, in research and practice.[16–25,28] The Medication Non-Adherence Scale (MNAS) has demonstrated good internal consistency reliability, and convergent and discriminant validity. Paper 1 and 2 also presented evidence for its concurrent and predictive validity in estimating PDC. The purpose of the current paper was to assess the comparative effectiveness of the MNAS and contemporary medication adherence, and medication adherence propensity scales, in predicting concurrent and future PDCs, respectively. The results presented here suggest that the MNAS performs better than the 5-point scale version of the 1986 Morisky Scale[17,39,55,56], the Medication Adherence Reasons Scale[17], and Adherence Estimator®[28].

Interpretation of Results

The MNAS was observed to perform better in estimating PDCs in both periods. It offered the highest R^2 values – 0.04 in the concurrent period and 0.08 in the predictive period; it explained 4.3% of the variation in patient-specific mean concurrent period PDC, and 8.3% of the

variation in patient-specific mean predictive period PDC. The MNAS had a standardized regression coefficient of -0.21 in the concurrent period and -0.29 in the predictive period. This indicates that for every standard deviation unit increase in the MNAS scale score, the value of the patient-specific mean PDC decreases by 0.21 standard deviation units in the concurrent period, and 0.29 standard deviation units in the predictive period. This decrease was lesser in the case of the comparator scales – 0.13 for the 5-point variant of the 1986 Morisky scale, 0.12 for the MAR-Scale, and 0.04 for the Adherence Estimator®. Though the 1986 Morisky scale and the MAR-Scale had inferior abilities to estimate mean PDC, these relationships were observed to be statistically significant. The Adherence Estimator® also demonstrated a statistically significant relationship with patient-specific mean predictive period PDC, but the MNAS offered higher standardized regression coefficients and R^2s. Furthermore, a comparison of the predictive abilities of the scales using the method proposed by Steiger[60] indicated that the estimates offered by the MNAS were statistically significantly better than those offered by 1986 Morisky Scale and MAR-Scale in predicting concurrent period PDCs, and those offered by the AE in predicting predictive period PDCs.

Limitations of the Study and Directions for the Future

This study was conducted among patrons of three independent community pharmacies in the Southeastern United States. This may limit the generalizability of the scale. Future researchers should apply the MNAS in various socio-demographic and geographic settings to assess its external validity. Though the current study is conducted among disease categories that are of primary interest to health care providers and payers, MNAS should also be tested in other disease conditions to further improve on its generalizability.

Though the MNAS performed better than the comparator scales, it is longer than the 1986 Morisky scale and the Adherence Estimator®, thus potentially more cumbersome to administer. A shorter scale is usually desired in a practice setting. Thus future researchers should develop 'short-form' variant of the MNAS to overcome this drawback of the scale.

Another observation that must be made based on the results presented here, is the low values of R^2 obtained for all self-reported measures in predicting PDCs. Considering the fact that the scale underwent multiple rounds of qualitative and quantitative pretest evaluations prior to this analysis minimizes the likelihood of the reason for such a result being unaccounted reasons for medication non-adherence or socially desirable response bias.[50] The authors believe that such a result may have been observed due to a lack of items that measure medication non-adherence due to over-dosing. PDC calculations not only account for gaps in fills, but also overlaps. Thus accounting for such over-dosing may improve the amount of variation explained in PDC. Future research should include an 'over-dosing' factor in the MNAS and reassess its concurrent and predictive validity against PDC.

Conclusion

This paper presented a comparative estimation of an adaptation of the concurrently measured National Committee for Quality Assurance (NCQA) proportion of days covered (PDC) measure of medication adherence by the Medication Non-Adherence Scale (MNAS), a 5-point version of the 1986 Morisky scale, and the Medication Adherence Reasons Scale (MAR-Scale). Results of a comparative prediction of the adapted future PDC measure by the MNAS and the Adherence Estimator® (AE) were also described here. These analyses provided evidence for the statistical superiority of the MNAS in estimating both, concurrent and future, medication

adherence (as measured by the adapted PDC measure), over the other scales used in this study. Based on these results, and those obtained by Athavale et al in the MNAS developmental papers[50,51], the Medication Non-Adherence Scale offers health care practitioners and researchers a valuable tool to improve patient health.

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LIST OF APPENDICES

APPENDIX A

Table 1

Description of sample demographic characteristics

Demographic Characteristics		Concurrent Period		Predictive Period	
		#	%	#	%
Age	<= 45	43	6.5%	34	5.9%
	46 – 60	196	29.4%	174	30.1%
	61 – 70	192	28.8%	172	29.7%
	71 – 80	157	23.6%	136	23.5%
	> 80	78	11.7%	63	10.9%
Gender	Male	223	33.5%	190	32.8%
	Female	375	56.3%	332	57.3%
	Missing	68	10.2%	57	9.8%
Race	White	583	87.5%	500	86.4%
	Other races	81	12.2%	76	13.1%
	Missing	2	0.3%	3	0.5%
Education	Up to high school graduate	270	40.5%	240	41.5%
	Some college (no degree), trade or technical school, or associate degree	215	32.3%	192	33.2%
	Bachelors, professional, or graduate degree	175	26.3%	142	24.5%
	Missing	6	0.9%	5	0.9%
Marital Status	Married	431	64.7%	375	64.8%
	Currently not married	234	35.1%	203	35.1%

	Missing	1	0.2%	1	0.2%
Income	Under $20,000	161	24.2%	150	25.9%
	$20,000 to $39,999.99	161	24.2%	132	22.8%
	$40,000 to $59,999.99	94	14.1%	82	14.2%
	$60,000 to $79,999.99	64	9.6%	56	9.7%
	$80,000 or more	141	21.2%	117	20.2%
	Missing	45	6.8%	42	7.3%
No. of Medications	1 – 2	83	12.5%	60	10.4%
	3 – 4	165	24.8%	139	24.0%
	5 – 6	165	24.8%	143	24.7%
	7 – 8	108	16.2%	97	16.8%
	9 – 10	55	8.3%	50	8.6%
	> 10	67	10.1%	69	11.9%
	Missing	23	3.5%	21	3.6%
Health Insurance	Medicare	388	56.6%	339	49.5%
	Medicaid	71	10.4%	66	9.6%
	Private	424	61.9%	364	53.1%
	Uninsured	37	5.4%	33	4.8%
	Tricare	9	1.3%	6	0.9%
	Don’t know	7	1.0%	6	0.9%
	Missing	4	0.6%	4	0.6%
Health Status	Excellent	20	3.0%	16	2.8%

	Very Good	169	25.4%	137	23.7%
	Good	265	39.8%	229	39.6%
	Fair	171	25.7%	158	27.3%
	Poor	39	5.9%	37	6.4%
	Missing	2	0.3%	2	0.3%

APPENDIX B

Table 2

Comparative effectiveness of the MNAS with contemporary scales

	Scales	R^2	Std. Reg. Coef.	*p* value
Concurrent Period	MNAS	0.04	-0.21	<0.01
	5-point 1986 Morisky Scale	0.02	-0.13	<0.01
	MAR-Scale	0.02	-0.12	<0.01
Predictive Period	MNAS	0.08	-0.29	<0.01
	AE	0.01	-0.10	0.02

[*] Adherence Estimator is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA. US and non-US Patents Pending.

[†] This was done to ensure that patient identifiers were not exposed to the researchers, and to abide with Health Insurance Portability and Accountability Act (HIPAA)[62] regulations.

[‡] Each month was assumed to be 30 days long.

[§] This categorization was based on that proposed by McHorney[28], where a score is '0' is categorized as 'low risk for adherence problems', '2-7' as 'medium risk for adherence problems', and '8+' as 'high risk of adherence problems'.

[**] This model was also run specifying the categorized Adherence Estimator® score as a categorical variable in the model. This resulted in an R^2 of 0.03.

CHAPTER V:

DISCUSSION

OVERVIEW

The purpose of this chapter is to discuss the findings and implications of this dissertation. First, results of reliability and validity testing of the Medication Non-Adherence Scale (MNAS) and the Medication Non-Persistence Scale (MNPS), and suggestions for their use in health care practice, will be elaborated. Following this, limitations of the methodology used here, and some directions for future research, will be discussed. This chapter will end of a brief conclusion for this dissertation project.

KEY FINDINGS AND SUGGESTIONS FOR USE IN HEALTH CARE PRACTICE

Medication Non-Adherence Scale

The primary goal of this dissertation was to develop a health care practice setting administrable, disease non-specific scale for medication non-adherence that can distinguish between different reasons for non-adherence. Such a scale would not only have the ability to estimate concurrent medication non-adherence, but also future non-adherence. The results presented in this document offer evidence for the achievement of these goals. Six and three month adaptations of the National Committee for Quality Assurance (NCQA) proportion of days covered (PDC) measure[1] were used as criterion measures to concurrently and predictively validate the MNAS. The NCQA PDC measure is recommended, and used, by certain payers to enhance reimbursement to health care practitioners. Thus based on the ability of this scale to estimate PDC, if used in the practice setting, the MNAS may allow practitioners to identify patients that need medication adherence management, improve their performance measures, and thus enhance their reimbursement from payers[2]. A confirmatory factor analysis showed that the MNAS can be divided into five sub-scales that offer reasons for the non-adherence – intentional non-adherence due to worries about side-effects, intentional non-adherence due to worries about addiction, intentional non-adherence due to worries about cost, intentional non-adherence due to lack of perceived need for the medication, and unintentional non-adherence. The scores obtained on these sub-scales can be used by health care practitioners to implement appropriate

interventions to improve their patients' medication adherence, and thus also reimbursement from payers.

The MNAS is a sixteen item scale, measured on a five-point scale with options 'Never'. 'Rarely', 'Sometimes', 'Often', and 'Always', scored from 1 through 5. If a patient presents with a summated score of more than 16 on the scale, the person administering the scale must study the responses on individual items to identify potential reasons for non-adherence. Such a score may indicate a PDC of less than 95% in the past 6 months. A summated score of greater than 20 on the scale may indicate a higher propensity of non-adherence in the next three months (i.e. a PDC of less than 95%) as well. In order to improve medication adherence, appropriate interventions should then be implemented based on the patient's performance on the sub-scales.

Besides demonstrating good psychometric properties, the MNAS was also seen to perform better than some of the currently used medication adherence and medication adherence propensity scales. Specifically, this dissertation compared the concurrent PDC estimating ability of the MNAS with the five-point variant of the 1986 Morisky scale[3–6] and the Medication Adherence Reasons Scale (MAR-Scale)[3,4], and its predictive PDC estimating ability against the Adherence Estimator® (AE)[7]. Based on our results, the MNAS outperformed all of these scales in estimating the criterion measures considered.

Medication Non-Persistence Scale

This dissertation also aimed at developing a multi-item self-reported measure for medication non-persistence. The evidence presented in this document outlines a successful endeavor. This process was exploratory in nature, as based on our literature review, currently there are no multi-item instruments that help identify reasons for non-persistence. A series of

both, qualitative and quantitative, pretest were conducted to arrive at a set of items for this scale. A confirmatory factor analysis revealed a single factor solution for the Medication Non-Persistence Scale (MNPS). In its final version, the MNPS is a nine item scale, designed to obtain binary 'yes' or 'no' responses on each item. Each 'yes' response receives a score of '1', and each 'no' response a score of '0'. The MNPS was validated against a standardized patient-specific mean days to discontinuation measure. The result of a ROC curve analysis concluded that a summated score greater than zero may indicate non-persistence. If such a score is obtained, the person administering the scale must inspect the individual items to identify the reason(s) for non-persistence.

LIMITATIONS OF THE STUDY AND DIRECTIONS FOR FUTURE RESEARCH

The first limitation of this study is potentially low external validity. The study was conducted among patrons of three independent community pharmacies in the Southeastern United States, thus potentially limiting its generalizability to other socio-demographic and geographic populations. Future research should apply the MNAS and the MNPS in a variety of settings to test their external validity. This will further strengthen the evidence for reliability, validity, and applicability of the scales.

The MNAS underwent multiple rounds of qualitative and quantitative pretests. But the amount of variation explained in the concurrent PDC measure was observed to be low (5.87%). Based on the results of Pretest 3 in Paper 1, the likelihood of observing this result due to socially desirable response bias seems unlikely. This may have been observed because of a missing factor in the scale; medication non-adherence is not only comprised of under-dosing, but also over-dosing. Most scales, including the MNAS, only assess under-dosing.[*] Future research should address this aspect of non-adherence by adding a factor that measures over-dosing, and identifies reasons for the same. This may help improve the amount of variation explained in the concurrent measurement of PDC.

The results of tests for studying concurrent and predictive validity of the MNAS indicated that current medication-taking behavior may help predict future medication-taking behavior. This may indicate that medication adherence has certain trait-like aspects. But a lot of

the variation in future medication-taking behavior (about 89%) was not explained by the MNAS. Such a result may indicate presence of state- or occasion-like factors within the construct. Future research should study the work published by Cole and colleagues in their development of the Trait-State-Occasion Model[8] and the Latent Trait-State-Occasion Model[9], and apply it to the context of medication adherence.

A scale developed for use in the clinical practice setting should ideally be short to administer. Though the MNAS offers more functionality, better psychometric properties, and more effective estimation of the PDC than some of the contemporary scale (e.g. 1986 Morisky scale[10], Morisky Medication Adherence Scale[11], MAR-Scale[3], the Adherence Estimator®[7], etc.), it is longer than most scales currently used in practice. Its length may increase the burden on the person administering the survey (e.g. pharmacist, pharmacy technician, nurse, etc.). Future researchers should make an attempt at developing a 'short-form' version of the MNAS to reduce administration times.

CONCLUSIONS

Despite the strong evidence for detrimental effect of medication non-adherence and non-persistence[12–16], there are quite a few issues with the effective measurement of these constructs in clinical practice. There are no multi-item instruments to measure medication non-persistence in clinical practice today. Paper 1 presented evidence for the reliability and validity of such an instrument – the Medication Non-Persistence Scale (MNPS). Besides estimating days to discontinuation, and helping identify individuals who may have discontinued their medication in the past year, the MNPS items also offer reasons for the discontinuation.

There are numerous instruments available to measure medication adherence, but some instruments do not possess good psychometric properties (e.g. 1986 Morisky scale[10]), some offer different factor structures across diseases (e.g. MAR-Scale[3]), some use different scales for a part of their items (e.g. RAM scale[17]), while some require the patients to remember minute details about the medications that they are taking (Diagnostic Adherence to Medications Scale (DAMS)[18]. The Medication Non-Adherence Scale (MNAS) has been designed to be disease non-specific, and relatively easy to administer in a practice setting. Paper 1 demonstrated evidence for its internal consistency reliability, convergent, discriminant and concurrent validity, and ability to distinguish between five reasons for medication non-adherence – worries about side-effects, worries about addiction to the medication, worries about medication cost, lack of perceived need for the medication, and unintentional non-adherence. Paper 2 offered evidence

for its ability to predict future medication non-adherence. Moreover, the MNAS has been concurrently and predictively validated against adaptations of the National Committee for Quality Assurance (NCQA) proportion of days covered (PDC) measure[1]. This measure is used by the Centers for Medicare and Medicaid Services (CMS), and some private payers, to determine health care quality and reimbursement.[2] Paper 3 concluded that the MNAS was more effective in estimating concurrent PDC as compared to the 1986 Morisky scale[5,6,10] and the MAR-Scale[3], and future PDC as compared to the AE[7]. Thus, the MNAS is a worthy candidate for an instrument to identify cases of medication non-adherence, predict its future occurrence, and distinguish between reasons for non-adherence, in a clinical practice setting.

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[*] Items measuring over-dosing were initially included in the MNAS, but were dropped in the final version as they reduced its internal consistency reliability.

VITA

Summary

Amod S. Athavale is currently a doctoral candidate in the Department of Pharmacy Administration at the University of Mississippi, working towards a PhD in Pharmaceutical Sciences (Emphasis: Pharmacy Administration). He has a Bachelor of Pharmacy degree from Mumbai University (Mumbai, Maharashtra, India) and an MS in Pharmacy Administration degree from the University of Mississippi (University, MS, USA). He has worked as a Research Assistant at the Center for Pharmaceutical Marketing and Management at the University of Mississippi for six years. His research interests include studying patient, physician and pharmacist behavior, product adoption, promotion, and pharmacoepidemiology and health outcomes research.

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Thesis: The measurement of pharmacy loyalty and its use in the development of marketing strategies for the RxSync Service^{SM}

Chair: Dr. Benjamin F. Banahan, III

Committee members: Dr. John P. Bentley and Dr. Donna S. West-Strum

Bachelor of Pharmacy, University of Mumbai, Mumbai, Maharashtra, India – August 2008

Professional Experience

Dissertation Fellow, Graduate School, UM, MS (August 2014 – December 2014)

Research Assistant, Mississippi Medicaid Drug Utilization Review (MS-DUR) at the Center for Pharmaceutical Marketing and Management (CPMM) at the University of Mississippi (UM), MS (January 2013 – July 2014)

- Lead SAS programmer for the development of an exceptions monitoring architecture.
- Assessment of prescription medication utilization and health care quality.

Research Assistant, School of Pharmacy, UM, MS (August 2008 – July 2012):

- *With Center for Pharmaceutical Marketing and Management (CPMM):*

  Assessment of pharmacy and health care quality measures in the Mississippi Medicaid data.

  Assessment of utilization and prescribing patterns of pharmaceuticals and identification of issues with the same, using the National Medicaid, and 5% National Medicare data
- *With The University of Mississippi Office of Research Technology Transfer:*

  Conduct current pharmaceutical market and pipeline analyses; conduct pharmaceutical and equipment patent searches; write reports on market potential for new chemical moieties.
- *With the Department of Pharmacy Administration:*

  Collaborate with faculty in assessing issues like medication non-adherence, primary medication non-adherence (PMN), etc.

Teaching Assistant, School of Pharmacy, UM, MS (August 2011 – December 2011; August 2012 – December 2012):

- Assist in teaching the Information Skills in Pharmacy Practice (PRCT 350) course.

Project Associate (Intern), BioVid Corporation, Princeton, NJ (May 2011 – August 2011):

- Assist researchers in conducting primary and secondary pharmaceutical market research, i.e., analyzing physician and patient survey, patient record and IMS data, creating project report presentations, etc.

Research Fellow, CPMM, UM, MS (June 2010 – May 2011):

- Collaborate with faculty to study the impact of various clinical and health policy issues on health and economic outcomes using Medicare and Medicaid health insurance claims data.

Summer Intern, NuMed Labs, Pvt. Ltd, Vasai, Maharashtra, India (May 2007 – August 2007)

- Obtain a general overview of the operations in a pharmaceutical company.

Research Experience

Athavale AS, Banahan BF III, Bentley JP, West-Strum DS, Antecedents and consequences of pharmacy loyalty behavior, International Journal of Pharmaceutical and Healthcare Marketing; 2015;Vol.9,Iss.1

Athavale AS, Null KD, Banahan BF, Clark J, Defining specialty drugs: an environmental scan and comparison of specialty drug lists, Academy of Managed Care Pharmacy 26th Annual Meeting and Expo, Tampa, FL, 1-4 April, 2014

Athavale AS, Banahan BF III, Hardwick SP, Clark JP, Are you counting prescription medication utilization correctly? International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting, Washington, DC, 2-6 June, 2012

Datar M, Athavale AS, Banahan BF III, Multiple sclerosis and depression: a case-control study among Medicare beneficiaries, Annual Drug Information Association Meeting, Chicago, IL, 19-23 June 2011

Athavale AS, Banahan BF III, Mendonca CM, Impact of potential drug-drug interactions (DDIs) on health outcomes and cost to Medicaid: the monetary benefits of quality health care, International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting, Baltimore, MD, 21-25 May 2011

Dharmarajan S, Yang Y, Athavale AS, Bentley JP, Null KD, Banahan BF III, Risk of hospitalization for pneumonia associated with the use of atypical versus typical antipsychotics in a national sample of Medicare beneficiaries, International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting, Baltimore, MD, 21-25 May 2011

Dharmarajan S, Yang Y, Athavale AS, Bentley JP, Null KD, Banahan BF III, Risk of hip fractures in elderly Medicare beneficiaries using atypical or typical antipsychotics: a propensity score analysis, International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting, Baltimore, MD, 21-25 May 2011

Dharmarajan S, Yang Y, Athavale AS, Bentley JP, Null KD, Banahan BF III, Risk of hospitalizations for venous thromboembolism in atypical vs. typical antipsychotic users in a national sample of Medicare beneficiaries: a claims data analysis, International

Society for Pharmacoeconomics and Outcomes Research Annual International Meeting, Baltimore, MD, 21-25 May 2011

Banahan BF III, Mendonca CM, Athavale AS, Bentley JP, Incidence and outcomes of potential drug-drug interactions between ACE/ARBs and potassium sparing diuretics, International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting, Atlanta, GA, 15-19 May 2010

Athavale AS, Lokhandwala TT, Datar MV, West-Strum DS, An analysis of FDA untitled and warning letters, 2009-2012, The Pharmaceutical Marketing Research Group Institute Meeting, Jersey City, NJ, 20-22 October, 2013

Athavale AS, Bentley JP, Banahan BF III, Thinking longitudinally: adding the fourth dimension to your research, The Pharmaceutical Marketing Research Group Institute Meeting, Philadelphia, PA, 14-16 October, 2012

Bentley JP, Adcock KG, Dikun JA, Athavale AS, Do pharmacy students read exam instructions? American Association of Colleges of Pharmacy Annual Meeting, Kissimmee, FL, 14-18 July, 2012

Athavale AS, Banahan BF III, Bentley JP, West DS, Identification of patient loyalty segments (PLSs) in development of marketing strategies for pharmacies, American Pharmacists Association Annual Meeting, Seattle, WA, 25-28 March 2011

Athavale AS, Lokhandwala T, Padwal T, Verma S, Jariwala K, Banahan BF III, Holmes ER, Comparing patients' compliance attitudes and behaviors with their perceived value for RxSync Service^{SM} components, American Pharmacists Association Annual Meeting, Washington, DC, 11-15 March 2010

Verma S, Athavale AS, Lokhandwala T, Padwal T, Jariwala K, Banahan BF III, Holmes ER, An assessment of perceived value and willingness to pay for RxSync ServiceSM, American Pharmacists Association Annual Meeting, Washington, DC, 11-15 March 2010

Awards and Honors

Graduate School Dissertation Fellowship, Graduate School, UM, MS (August 2014)

Full Scholarship for Graduate Education, Center for Pharmaceutical Marketing and Management and the Department of Pharmacy Administration, UM, MS (August 2008 – July 2014)

Graduate Students Council Research Grant recipient, UM, MS (June 2014)

Platinum award for podium presentation at the Academy of Managed Care Pharmacy's 26th Annual Meeting & Expo, Tampa, FL, 1-4 April, 2014

Contributor at the Poster Session, The Pharmaceutical Marketing Research Group Institute Meeting, Jersey City, NJ, 20-22 October, 2013

Contributor at the Poster Session, The Pharmaceutical Marketing Research Group Institute Meeting, Philadelphia, PA, 14-16 October, 2012

International Society for Pharmacoeconomics and Outcomes Research Distinguished Service Award (June 2012)

Who's Who Among Students in American Universities & Colleges® (January 2012)

Research Fellowship, CPMM, University of Mississippi, University, MS (June 2010 – May 2011)

Inducted into Rho Chi – The Academic Honors Society in Pharmacy (April 2010)